Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis

Running title: Metabolically-defined body size phenotypes and CHD

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Abstract (238 words)

Aims: The hypothesis of "metabolically healthy obesity" implies that, in the absence of metabolic dysfunction, individuals with excess adiposity are not at greater cardiovascular risk. We tested this hypothesis in a large pan-European prospective study.

Methods and results: We conducted a case-cohort analysis in the 520,000-person European Prospective Investigation into Cancer and Nutrition study ("EPIC-CVD"). During median follow-up of 12.2 years, we recorded 7,637 incident coronary heart disease (CHD) cases. Using cut-offs recommended by guidelines, we defined obesity and overweight using BMI, and metabolic dysfunction ("unhealthy") as ≥3 of elevated blood pressure, hypertriglyceridemia, low HDL-cholesterol, hyperglycemia, elevated waist circumference. We calculated hazard ratios (HRs) and 95% confidence intervals (95% CI) within each country using Prentice-weighted Cox proportional hazard regressions, accounting for age, sex, centre, education, smoking, diet and physical activity. Compared to metabolically healthy normal weight people (reference), HRs were 2.15 (95%CI: 1.79; 2.57) for unhealthy normal weight, 2.33 (1.97; 2.76) for unhealthy overweight, and 2.54 (2.21; 2.92) for unhealthy obese people. Compared to the reference group, HRs were 1.26 (1.14; 1.40) and 1.28 (1.03; 1.58) for metabolically healthy overweight and obese people, respectively. These results were robust to various sensitivity analyses.

Conclusion: Irrespective of BMI, metabolically unhealthy individuals had higher CHD risk than their healthy counterparts. Conversely, irrespective of metabolic health, overweight and obese people had higher CHD risk than lean people. These findings challenge the concept of "metabolically healthy obesity", encouraging population-wide strategies to tackle obesity.

Keywords: Coronary Heart Disease; Adiposity; Obesity; Metabolic syndrome; Epidemiology

Introduction

Overall and abdominal obesity, commonly measured by body mass index (BMI) and waist circumference (WC), are important risk factors for coronary heart disease (CHD) (1-3). The effects of obesity on CHD are thought to be largely mediated by other cardiometabolic risk factors such as insulin resistance, atherogenic dyslipidemia, and type 2 diabetes (4). However, many obese people have few or no elevated metabolic risk factors included in the definition of the Metabolic Syndrome (MetS) (5), suggesting that there may be a group of obese people – the "metabolically healthy obese" – who are not at higher cardiovascular risk (6). There is no consensus on the criteria to define this subtype, and an estimated 3 to 57% of obese individuals are considered "metabolically healthy obese" depending on the population under study and the definition used (7). There has been conflicting evidence on whether metabolically healthy obese people are at higher risk of cardiovascular disease (CVD) or type 2 diabetes (8-17), with recent meta-analyses challenging the concept of the metabolically healthy obesity by showing higher cardiovascular risk among obese individuals with no metabolic syndrome (14, 15, 17, 18). The existence of "metabolically healthy obesity" has also been questioned by the latest European Society of Cardiology (ESC) guidelines for CVD prevention (19). However, previous studies have been limited by incomplete adjustment for potentially important confounders (such as physical activity and smoking), short duration of follow-up (and hence small numbers of incident CHD events) and use of composite outcomes, such as all-cause mortality. More powerful and detailed studies with precisely defined outcomes are therefore needed to clarify the association with CHD risk, since heterogeneous effects of obesity according to metabolic health could have important implications for risk prevention strategies.

To address this, we analysed 7,637 incident CHD cases recorded during 12.2 years of follow-up from the European Prospective Investigation into Cancer and Nutrition cardiovascular disease (EPIC-CVD) case-cohort study. Our primary aim was to examine the separate and combined associations of obesity and metabolic health with CHD.

Methods

Study population

EPIC-CVD is a prospective case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Briefly, EPIC includes 366,521 women and 153,457 men, mostly aged 35 to 70 years old at baseline, recruited between 1991 and 1999 at 23 centres across 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Adults were invited from the local general population except in the French centre (women in a national health insurance plan), some Italian and Spanish centres (recruited through local blood donor associations), Utrecht (The Netherlands) and Florence (Italy) (women invited for population-based breast cancer screening programmes) and Oxford (UK) (specifically recruited a substantial proportion of vegetarians). At baseline, participants gave a blood sample and completed questionnaires on diet, lifestyle, and medical history. Detailed baseline characteristics of the EPIC cohort have been previously described (20).

A case-cohort study nested in a large prospective cohort is similar to a nested case-control study with the difference that a random subcohort is selected for use as a reference group, rather than matched controls. This design is efficient as it does not require all study participants to have exposure measurement and has the advantages of a longitudinal cohort study with prospective assessment of key exposures that are not subject to recall bias. Unlike the nested case-control design, it allows risk to be measured at any time until the end of follow-up and permits time-to-event analysis (21). A representative random subcohort of 18,249 participants (62% women), stratified by centre, was selected for the EPIC-CVD project, constituting a case-cohort design. After exclusion of 609 participants with a prior history of myocardial infarction or stroke at baseline, 17,640 subcohort members remained. In total in the EPIC study, 13,964 incident CHD cases developed during follow-up, of whom 631 belong to the subcohort. Ethical review boards of the International Agency for Research on Cancer and all local institutions where participants had been recruited gave approval for the original EPIC study, and all participants gave written informed consent.

Blood pressure measurements were not available for the centres in Norway, Asturias, or Navarra, and WC was not recorded in Norway and Umea (22). These centres were excluded from the analyses, as well as the French centre due to the limited number of incident CHD events (n=41). Further exclusions were performed based on missing exposure and covariate data, described

below. All analyses were performed in a sample restricted to participants with no missing data (complete-case analysis). Because exclusions due to missing data may result in a selected sample, we also used a multiple imputation approach as a sensitivity analysis to compare the results with the complete-case approach. A schematic representation of the EPIC-CVD case-cohort design and sample selection is given in **Supplemental Figure 1**.

Definitions of obesity and metabolic disorders

Trained health professionals measured blood pressure (BP) (23), weight, height, and waist circumference (WC) (24), except in the France and Oxford centres where body size measurements were self-reported (25). BMI was calculated as weight (kg) divided by the square of height (m^2). Obesity was defined according to the World Health Organization (26) as BMI≥30 kg/m^2, overweight as 25≤BMI<30 kg/m^2, and normal weight as 18.5≤BMI<25 kg/m^2. Underweight (BMI<18.5) participants were excluded due to the limited number (n=264, less than 1% of the subcohort).

Total cholesterol, HDL-cholesterol, triglycerides, and glucose were measured in baseline serum samples on a Roche auto-analyser (Roche diagnostics, USA) and HbA1c was measured in the erythrocyte fraction using the Tosoh-G8 HPLC analyser (Tosoh Bioscience, Japan) at Stichting Huisartsen Laboratorium (Etten-Leur, Netherlands). Fasting status was available for 87% of participants. Metabolic Syndrome (MetS) was defined according to the 2009 Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (5) as having three or more of the following metabolic abnormalities: 1) elevated BP, defined as systolic BP≥130 and/or diastolic BP≥85 mm Hg and/or use of antihypertensive medication at baseline and/or self-reported history of hypertension; 2) hypertriglyceridemia, defined as triglycerides≥1.7mmol/L (150mg/dL) or current use of lipid-lowering medication at baseline; 3) low HDL-cholesterol, defined as <1.0mmol/L (40mg/dL) for men and <1.3mmol/L (50mg/dL) for women; 4) hyperglycemia, defined as fasting blood glucose ≥5.6mmol/L (100mg/dL) or non-fasting blood glucose≥7.8mmol/L (140mg/dL, with fasting defined as ≥3 hours between last meal and blood draw (27)), and/or current use of antidiabetic medication at baseline and/or self-reported history of diabetes; or 5) elevated waist circumference, defined as WC≥94cm for men and WC≥80cm for women. Where information on fasting status was not available (23% of participants), the non-fasting cut-off was used for glucose. Diabetes was defined as a self-reported history and/or HbA1c≥6.5%.

Covariate definition

Validated questionnaires were used to obtain information on education, smoking habits, dietary intake (including alcohol intake), and physical activity at study baseline. The Cambridge Index of physical activity was derived by combining occupational with recreational activity level to produce four groups: active, moderately active, moderately inactive and inactive (28). Usual diet over the previous 12 months was assessed using validated country/centre-specific dietary questionnaires (24), allowing the calculation of food group, individual energy and nutrient intakes (derived from the EPIC nutrient database (29)). To summarize diet quality for adjustment purposes, we computed a Mediterranean diet score, ranging from 0-18, with greater scores given to higher intakes of fruit, vegetables, legumes, nuts, grains, and fish, lower intakes of red meat and dairy, and moderate intake of alcohol (30).

Outcome ascertainment

Incident CHD cases were defined as first CHD events, whether non-fatal or fatal, consisting of ICD-10 codes I20-I25, which include myocardial infarction, other acute ischemic heart diseases, chronic ischemic heart disease and angina pectoris (31). EPIC centres used methods including self-report, linkage to primary and secondary care registers, hospital admissions and mortality data to ascertain events. Non-fatal CHD events were further validated by additional review of individual medical records and/or linkage with registries with validation rates ranging from 82% to 100% (32), while fatal CHD events were generally ascertained through mortality registries. End of follow-up for CHD events varied between centres and ranged between 2003 and 2010. Participants known to have left the country were considered lost to follow-up and censored at their date of last follow-up.

Statistical analyses

Characteristics of participants in the subcohort were described across body size phenotypes and compared using ANCOVA, giving adjusted least square means and percentages (and confidence interval) across the six phenotypes. Adjustments were made for centre, sex, age, education, smoking status and energy intake (for description of dietary intake only).

To assess the association of adiposity markers and metabolically-defined body size phenotypes with incident CHD, we used Prentice-weighted Cox proportional hazards models with robust standard errors to account for the case-cohort design (21). Age was the underlying time scale, with entry time defined as the participant's age at recruitment and exit time as age at first fatal or

non-fatal CHD event or censoring (whichever came first). For all analyses, we stratified the models by sex and centre. To account for the multi-country design, we followed a 2-stage approach where models were fitted separately within country and then country-specific HRs were combined using multivariate random-effects meta-analysis (33).

To assess the shape of associations of BMI and WC with CHD risk, country-specific HRs were calculated by comparing quintiles (defined using all participants) of baseline adiposity values with the lowest quintile. The pooled hazard ratios were then plotted against mean values of the adiposity measure within each quintile, accompanied by a group-specific confidence interval derived only from the variance of the log risk in that category (including the reference quintile) (34). As associations were approximately log-linear, we calculated HRs associated with 1 standard deviation (SD) higher baseline value (4.10 kg/m^2 for BMI, 12.7 cm for WC). Heterogeneity between countries was quantified using the I^2 statistic (35).

For analyses of adiposity measures, Model 0 was adjusted for baseline age and smoking status (never, former, current). Model 1 was further adjusted for highest educational level (no schooling/primary, secondary, vocational/university), physical activity, Mediterranean diet score, energy and alcohol intake. Model 2 was further adjusted for the different body size markers, i.e. WC for BMI and BMI for WC. In Model 3, to explore biological pathways potentially underlying the associations, we adjusted for baseline age, smoking status, and intermediate cardiovascular risk factors: blood cholesterol (total and HDL), systolic blood pressure and diabetes. Interactions on the multiplicative scale between BMI and WC and between BMI and MetS were formally tested.

For analyses of metabolically-defined body size phenotypes, Model A was adjusted for baseline age, smoking status (never, former, current) and highest educational level (no schooling/primary, secondary, vocational/university). To investigate the potential mediating effect of lifestyle habits (36, 37) on the association between metabolically-defined body size phenotypes and CHD risk, we compared Model A to Model B, which further included adjustment for physical activity (Cambridge index: inactive, moderately inactive, moderately active, active), alcohol consumption (g ethanol/day), Mediterranean diet score and energy intake (kcal/day).

The primary complete-case analyses included only participants with non-missing data on anthropometric measurements, blood pressure, blood biomarkers and all covariates, with sensitivity analyses that maximised the number of participants by only excluding those with missing data on the covariates in each analysis model. Additional sensitivity analyses performed

were: 1) excluding the first 2 years of follow-up to minimise the potential for reverse causality; 2) including only "hard" CHD events, i.e. myocardial infarction and coronary death; 3) including only events validated with a high level of certainty; 4) restricting analyses to "never smokers" only, to apply more rigid control for smoking; 5) separately for men and women to investigate potential differences by sex. For comparability with other studies, we also performed sensitivity analyses with different definitions of obesity or metabolic health: 6) excluding the WC criterion from the definition of MetS, modifying the definition of metabolically healthy to be <2 abnormalities (17, 38); 7) defining metabolically healthy participants as having none of four possible abnormalities (elevated blood pressure, triglyceridemia, hyperglycemia, low HDL-cholesterol); 8) using abdominal obesity index defined as WC≥102cm for men and WC≥88cm for women. For the latter, a model (Model C) was fitted including BMI as a continuous covariate. Finally, 9) we used a multiple imputation approach to impute the missing values for the non-systematically missing variables (i.e. after exclusion of the centres with no data on blood pressure or waist circumference). Five imputed datasets were generated and estimates were combined using Rubin's rules.

All analyses were performed with SAS 9.3 (SAS Institute, Cary, NC) and STATA MP 13.1. We summarize the key aspects of the modelling strategy in **Supplemental Figure 2**.

Results

After exclusions, there were 10,474 subcohort participants and 7,637 incident CHD cases (394 of whom are also in the subcohort) comprising a total of 17,733 participants who contributed 117,829 person-years at risk in the complete-case analysis. 63% of subcohort participants were female and the mean (SD) age and BMI were 53.6 (9.3) years and 26.1 (4.1) kg/m^2 respectively (**Table 1**). Median follow-up was 12.2 years (interquartile range: 9.7 – 13.6). 15.8% of subcohort participants were obese, 25.6% had MetS, whilst 45.2% of obese participants were "metabolically healthy". Metabolically healthy obese participants were younger and had lower BMI than obese participants with MetS (p<0.0001). The metabolically healthy obese had worse metabolic parameters (higher lipid levels, blood pressure, HbA1c, C-reactive protein), had higher red meat intake, were less likely to be current smokers, more likely to be inactive and less educated than metabolically healthy normal weight participants (all p<0.0001, **Table 1**). The proportion of obese participants ranged from 11% in the UK to 30% in Greece and the proportion of obese participants who were metabolically healthy ranged from 31.7% in Germany to 57.9% in Spain (**Supplemental Table 1**).

Associations between body size and CHD

There was a positive approximately log linear association between BMI and CHD risk (**Figure 1** and **Table 2**) after adjusting for potential confounders (Model 1): HR per-standard deviation = 1.25 (95% CI: 1.19, 1.32), p<0.0001. While the association was almost perfectly log-linear from quintile 1 to 4, departure from log-linearity was observed at the highest quintile. The risk of CHD almost doubled comparing the highest quintile (mean BMI = 32.7 kg/m^2) to the lowest quintile (mean BMI=21.5 kg/m^2) (HR=1.96 [95% CI 1.66, 2.32], p<0.0001). The association was substantially less strong after adjustment for WC (HR =1.06 [95% CI 0.97, 1.15], p=0.20), likely reflecting the effect of lean mass and peripheral adipose tissue. The association was also substantially attenuated in a model adjusted for intermediate cardiometabolic risk factors (blood pressure, total and HDL-cholesterol, diabetes) (HR =1.05 [95% CI 1.01, 1.10], p=0.03, **Table 2**). There was moderate heterogeneity across countries. Results were very similar in sensitivity analyses that use all available individuals with complete data for each model in turn (**Supplemental Table 2**). However, results with multiply imputed data showed that, despite being strongly attenuated, the HRs remained significant when adjusted for WC or for intermediate CVD risk factors (**Supplemental Table 3**). WC also had positive approximately linear associations with CHD (**Figure 1**, **Table 2**), which were robust to adjustment for BMI

(HR=1.24 [95% CI 1.10, 1.40], p<0.0001). Adjustment for cardiometabolic factors substantially attenuated the association (**Figure 1**, **Table 2**).

There was a significant interaction between BMI and WC (p=0.005), with a weaker association observed in the upper tertile of each anthropometric factor (**Figure 2**). For BMI, the HR per-standard deviation increase was 1.27 (95% CI 1.17, 1.38) in the lowest tertile of WC, whereas it was 1.10 (95% CI 1.03, 1.16) in the highest tertile. The association of WC with CHD was stronger at every level of BMI than any of the associations of BMI with CHD across the tertiles of WC: the HR per-standard deviation increase of WC was 1.65 (95% CI 1.43, 1.89) in the lowest tertile of BMI and 1.29 (95% CI 1.21, 1.38) in the highest tertile of BMI.

Associations between metabolically-defined body size phenotypes and CHD

Compared to the normal weight participants without MetS (reference group), all other metabolically-defined body size phenotypes were at significantly higher risk of CHD (**Figure 3**) in a fully adjusted model (Model B). Metabolically healthy obese individuals were at higher risk of CHD (HR=1.28 [95% CI 1.03, 1.58], p=0.02) but this was considerably lower than the risk in metabolically unhealthy groups. MetS was strongly positively associated with CHD risk, regardless of adiposity, with a HR of 2.15 (95% CI 1.79, 2.57: p<0.0001) for metabolically unhealthy normal weight participants with MetS and a HR of 2.54 (95% CI 2.21, 2.92: p<0.0001) in their obese counterparts. Results were generally consistent across countries (**Supplemental Figure 3; Figure 3)**. Similar results were obtained from models unadjusted for physical activity and diet (Model A): the HRs were 1.25 (95% CI 1.14, 1.38) and 1.27 (95% CI 1.03 – 1.57) in the healthy overweight and obese, and 2.17 (95% CI 1.82, 2.59), 2.35 (95% CI 2.02, 2.74) and 2.63 (95% CI 2.30, 3.01) in the unhealthy normal weight, overweight and obese, respectively. There were no significant interactions between BMI and MetS (p=0.19).

Sensitivity analyses show similar results after excluding the first 2 years of follow-up (**Supplemental Table 4**), when analyses were restricted to “harder” CHD events only (**Supplemental Table 5**), or when restricting the sample to non-smokers only (**Supplemental Table 6**). Analyses restricted to events only validated to the highest level of certainty were qualitatively similar but less precise (**Supplemental Table 7**). There was no difference between men and women (p for interaction=0.63, **Supplemental Table 8**). Estimates from the multiple imputation showed similar trends with the exception of an HR of greater magnitude for the metabolically healthy obese (1.67 [95% CI 1.39; 1.99]) (**Supplemental Table 3**).

Sensitivity analyses using a definition of MetS that excludes the WC criterion showed somewhat stronger positive associations for all phenotypes (**Supplemental Table 9**). Results were qualitatively similar to the main analysis (but less precise) when a stricter definition of metabolically healthy was used (i.e. having none of the MetS abnormalities) (**Supplemental Table 10**). Finally, when obesity was defined by WC (and not by BMI), and MetS did not include the WC criteria, HRs were again qualitatively similar to the main analysis although somewhat stronger (**Supplemental Table 11**). When further adjusted for BMI, HRs were attenuated. Agreement between the two definitions of metabolically-defined body size phenotypes where body size is defined by BMI or by WC was only moderate, with a weighted kappa of 0.667 (**Supplemental Table 12**).

Discussion

In this prospective case-cohort study with 7,637 CHD cases from 8 European countries followed-up for a median of 12.2 years, we assessed the separate and combined effects of body size and metabolic health on CHD. We observed higher CHD risk for general and central adiposity, as defined by BMI and WC, respectively. Whilst the effect of BMI was substantially attenuated on adjustment for WC, the effect of WC appeared to be robust to adjustment for BMI. Metabolically healthy overweight and obese individuals were at higher risk of CHD compared to their normal weight counterparts. However, CHD risk in metabolically unhealthy individuals was markedly higher than in their metabolically healthy counterparts across all BMI categories.

Our study, which is the largest to address this question in terms of the number of incident CHD events, suggests that "metabolically healthy" obesity is not a benign condition. This is of particular importance as overweight people (BMI ≥25 and <30) with no traditional cardiometabolic risk factors are not recommended for weight loss treatment by recent UK or US guidelines (39, 40). The risk of CHD in metabolically healthy overweight or obese individuals was significantly lower than in the "metabolically unhealthy" groups, suggesting that obese and overweight individuals without metabolic abnormalities are at intermediate cardiovascular risk between metabolically healthy normal weight individuals and metabolically unhealthy individuals. In support of this hypothesis, we showed that only 6% of the obese had strictly no cardiometabolic abnormality vs 31% of the normal weight, and that metabolically healthy obese individuals have worse cardiometabolic health than their normal weight counterparts, reflected by higher blood pressure, HbA1c, pro-atherogenic lipids, and C-reactive protein. These data concur with studies that used repeated measurements to evaluate the evolution of metabolically healthy obesity over time, showing that metabolically healthy obese people were more likely to go on to develop metabolic abnormalities (and become metabolically unhealthy obese) than their normal weight counterparts (41-47). Despite being acknowledged as a risk factor for cardiovascular disease, excess weight is not included in the prediction model SCORE (48). This algorithm estimates the 10 year risk of fatal CVD and its use is recommended by the ESC Guidelines for CVD risk assessment of patients to assist health professionals in their prevention and treatment strategies (19). Our results suggest that, even in the absence of multiple traditional CVD risk factors (smoking, type 2 diabetes, high blood pressure, high blood cholesterol), weight-loss strategies through intensive lifestyle advice (diet, exercise and behaviour modifications) or medical therapy (orlistat or bariatric surgery) should be recommended for obese patients to try to achieve and maintain a healthy body weight to decrease CVD risk.

Overall, these results support a population-wide strategy for prevention of obesity and overweight regardless of the initial metabolic status of individuals.

In accordance with previous evidence on CVD, type 2 diabetes, breast and colorectal cancer (14, 17, 49-51), normal weight individuals with metabolic abnormalities had twice the risk of normal weight individuals without metabolic abnormalities. This is consistent with the adverse effects of metabolic factors in cardiovascular health, which are independent of obesity and accumulation of fat, and could involve inflammation, high blood pressure, lipotoxicity and atherosclerosis (4, 52). We also found that a higher WC was associated with higher risk of CHD at all levels of BMI, including for those in the normal weight category. This is in line with pooled results from 11 prospective studies which found a linear positive association between WC and mortality risk at all levels of BMI ranging from 20 to 50 kg/m^2 (53), advocating for the importance of an increased waistline at whole spectrum of BMI. Furthermore, a growing body of literature based on novel imaging markers has shown heterogeneity in the cardiovascular phenotype of obesity depending on location of adipose depots, with increased risk observed with visceral adipose tissue compared to subcutaneous fat (54-56). This implies that targeted visceral fat loss, rather than overall weight loss, may be a more efficient treatment of obesity to prevent cardiovascular events. Medical therapy with orlistat, which leads to greater reduction in visceral adipose tissue compared to placebo in clinical trials (57, 58), is a treatment option recommended by the latest ESC guidelines (19).

Positive associations between BMI and WC and CHD are also consistent with previous evidence (1-4). Our study confirms both the shape and magnitude of a combined analysis of 39 prospective studies (5,259 CHD cases) by the Emerging Risk Factors Collaboration (3), which found a HR of 1.29 (1.22-1.37) for an increase in BMI of $4.56kg/m^2$ and 1.32 (1.24-1.40) for an increase in WC of 12.6cm. Our results also align with those of the recent study by the Global BMI Mortality Collaboration, which found a significantly higher risk of CHD death in both the overweight and obesity groups compared with the normal weight group in an analysis including 3,599,426 participants and 54,872 CHD deaths (1). Although substantially attenuated, an independent effect of BMI and WC remained after adjustment for major potential mediators (SBP, cholesterol, diabetes), indicating that the excess risk for CHD due to high BMI or WC is at least partially mediated by other factors. This is consistent with a pooled analysis of 97 prospective cohort studies from the Prospective Studies Collaboration (57,161 CHD cases), which estimated that these three factors collectively explained 46% of the excess risk due to

adiposity (4). The association between adiposity and CHD has been suggested to be causal by Mendelian randomization studies, which have shown that genetic scores indexing BMI or waist-to-hip ratio are associated with risk of CHD (59-61). Similar studies have shown causal associations of adiposity with cardiovascular risk factors, supporting the hypothesis of mediation by blood pressure and cholesterol (62).

Our study had various strengths, including its prospective design and its large sample size, allowing assessment of risk in various subgroups. Anthropometric factors were mostly measured by trained health professionals, which should reduce measurement error, and concomitant measurement of weight, height and waist circumference allowed direct comparison of BMI and WC in the same participants. The biomarkers measured and information on medical history permitted exploration of various commonly used definitions of metabolic syndrome, and the extensive information on covariates (smoking, physical activity, diet quality, alcohol, education) allowed adjustment for a range of potential confounders. However, we cannot rule out the possibility of unmeasured confounding. In particular, as behaviors like physical activity and diet are self-reported at a single time point and were therefore prone to measurement error (28, 63), it is likely that they were not fully captured.

Study limitations

A potential limitation when comparing our results with previous studies is the lack of consistency in the definition of metabolically healthy obesity (38, 64). Moreover, by definition, the MetS gives a simplified picture of diverse and complex phenotypes. To overcome this limitation, we chose the most common definition (14, 15, 17) (absence of the MetS (5)), and compared several alternative definitions in sensitivity analyses, all of which gave qualitatively similar results. The absence of repeated assessment of metabolic health or adiposity during follow-up meant we were unable to assess within-person variability in adiposity and shed light on the proportion of metabolically healthy obese individuals who became metabolically unhealthy, preventing analyses of “stable metabolically healthy obesity” and “transient metabolically healthy obesity”. Finally, we acknowledge that some of the centres included in the EPIC study are not representative of the general population, potentially limiting the generalizability of our findings. For example, the prevalence of metabolically healthy obesity within obese participants (45%) in EPIC-CVD is higher than in some other population-based studies (64), suggesting that EPIC participants are likely to be healthier than the general population. However, even if the participants are different from the general population, as long

as there is enough variability in the exposure (here, obesity and metabolic health markers), CHD risk estimates and generalizability of the associations are unlikely to be affected.

Conclusions

In this large pan-European study, overweight and obesity were associated with higher risk of CHD, even in the absence of metabolic syndrome. The presence of metabolic abnormalities was associated with a higher risk of CHD at all levels of adiposity, including in normal weight individuals. Overweight and obese individuals without metabolic dysfunction were at intermediate risk of CHD between healthy normal weight and metabolically unhealthy individuals. Our results highlight the importance of both obesity and metabolic health in CHD prevention and do not support the concept of “metabolically healthy obesity”. Population-wide prevention and treatment of obesity is therefore warranted, regardless of metabolic health.

Reference List

1. The Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;**388**(10046):776-786.

2. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;**373**(9669):1083-1096.

3. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011;**377**(9771):1085-1095.

4. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* 2014;**383**(9921):970-983.

5. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC, Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;**120**(16):1640-1645.

6. Phillips CM. Metabolically healthy obesity: Definitions, determinants and clinical implications. *Rev Endocr Metab Disord* 2013;**14**(3):219-227.

7. Plourde G, Karelis AD. Current issues in the identification and treatment of metabolically healthy but obese individuals. *Nutr Metab Cardiovasc Dis* 2014;**24**(5):455-459.

8. Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation* 2010;**121**(2):230-236.

9. Aung K, Lorenzo C, Hinojosa MA, Haffner SM. Risk of developing diabetes and cardiovascular disease in metabolically unhealthy normal-weight and metabolically healthy obese individuals. *J Clin Endocrinol Metab* 2014;**99**(2):462-468.

10. Flint AJ, Hu FB, Glynn RJ, Caspard H, Manson JE, Willett WC, Rimm EB. Excess weight and the risk of incident coronary heart disease among men and women. *Obesity (Silver Spring)* 2010;**18**(2):377-383.

11. Hinnouho GM, Czernichow S, Dugravot A, Nabi H, Brunner EJ, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. *Eur Heart J* 2015;**36**(9):551-559.

12. Ogorodnikova AD, Kim M, McGinn AP, Muntner P, Khan U, Wildman RP. Incident cardiovascular disease events in metabolically benign obese individuals. *Obesity (Silver Spring)* 2012;**20**(3):651-659.

13. Thomsen M, Nordestgaard BG. Myocardial infarction and ischemic heart disease in overweight and obesity with and without metabolic syndrome. *JAMA Intern Med* 2014;**174**(1):15-22.

14. Fan J, Song Y, Chen Y, Hui R, Zhang W. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: A meta-analysis of prospective cohort studies. *Int J Cardiol* 2013;**168**(5):4761-8.

15. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. *Ann Intern Med* 2013;**159**(11):758-769.

16. Sung KC, Ryu S, Cheong ES, Kim BS, Kim BJ, Kim YB, Chung PW, Wild SH, Byrne CD. All-Cause and Cardiovascular Mortality Among Koreans: Effects of Obesity and Metabolic Health. *Am J Prev Med* 2015;**49**(1):62-71.

17. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2016;**23**(9):956-966.

18. Zheng R, Zhou D, Zhu Y. The long-term prognosis of cardiovascular disease and all-cause mortality for metabolically healthy obesity: a systematic review and meta-analysis. *J Epidemiol Community Health* 2016;**70**(10):1024-1031.

19. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van D, I, Verschuren WM. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**(29):2315-2381.

20. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* 1997;**26 Suppl 1**:S6-14.

21. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika* 1986;**73**(1):1-11.

22. Haftenberger M, Lahmann PH, Panico S, Gonzalez CA, Seidell JC, Boeing H, Giurdanella MC, Krogh V, Bueno-de-Mesquita HB, Peeters PH, Skeie G, Hjartaker A,

Rodriguez M, Quiros JR, Berglund G, Janlert U, Khaw KT, Spencer EA, Overvad K, Tjonneland A, Clavel-Chapelon F, Tehard B, Miller AB, Klipstein-Grobusch K, Benetou V, Kiriazi G, Riboli E, Slimani N. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr* 2002;**5**(6B):1147-1162.

23. Schulze MB, Kroke A, Bergmann MM, Boeing H. Differences of blood pressure estimates between consecutive measurements on one occasion: implications for inter-study comparability of epidemiologic studies. *Eur J Epidemiol* 2000;**16**(10):891-898.

24. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondiere UR, Hemon B, Casagrande C, Vignat J, Overvad K, Tjonneland A, Clavel-Chapelon F, Thiebaut A, Wahrendorf J, Boeing H, Trichopoulos D, Trichopoulou A, Vineis P, Palli D, Bueno-de-Mesquita HB, Peeters PH, Lund E, Engeset D, Gonzalez CA, Barricarte A, Berglund G, Hallmans G, Day NE, Key TJ, Kaaks R, Saracci R. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;**5**(6B):1113-1124.

25. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. *Public Health Nutr* 2002;**5**(4):561-565.

26. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;**894**:i-253.

27. WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia - Report of a WHO/IDF consultation. Geneva: WHO Press; 2006.

28. Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr* 2003;**6**(4):407-413.

29. Slimani N, Deharveng G, Unwin I, Southgate DA, Vignat J, Skeie G, Salvini S, Parpinel M, Moller A, Ireland J, Becker W, Farran A, Westenbrink S, Vasilopoulou E, Unwin J, Borgejordet A, Rohrmann S, Church S, Gnagnarella P, Casagrande C, van Bakel M, Niravong M, Boutron-Ruault MC, Stripp C, Tjonneland A, Trichopoulou A, Georga K, Nilsson S, Mattisson I, Ray J, Boeing H, Ocke M, Peeters PH, Jakszyn P, Amiano P, Engeset D, Lund E, de Magistris MS, Sacerdote C, Welch A, Bingham S, Subar AF, Riboli E. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur J Clin Nutr* 2007;**61**(9):1037-1056.

30. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* 2014;**17**(12):2769-2782.

31. WHO. ICD-10 : International Statistical Classification of Diseases and Related Health Problems - 10th revision, edition 2010. Geneva, Switzerland: WHO Press; 2011. Report No.: Volume 2 - Instruction manual.

32. Danesh J, Saracci R, Berglund G, Feskens E, Overvad K, Panico S, Thompson S, Fournier A, Clavel-Chapelon F, Canonico M, Kaaks R, Linseisen J, Boeing H, Pischon T, Weikert C, Olsen A, Tjonneland A, Johnsen SP, Jensen MK, Quiros JR, Svatetz CA, Perez MJ, Larranaga N, Sanchez CN, Iribas CM, Bingham S, Khaw KT, Wareham N, Key T, Roddam A, Trichopoulou A, Benetou V, Trichopoulos D, Masala G, Sieri S, Tumino R, Sacerdote C, Mattiello A, Verschuren WM, Bueno-de-Mesquita HB, Grobbee DE, van der Schouw YT, Melander O, Hallmans G, Wennberg P, Lund E, Kumle M, Skeie G, Ferrari P, Slimani N, Norat T, Riboli E. EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. *Eur J Epidemiol* 2007;**22**(2):129-141.

33. Thompson S, Kaptoge S, White I, Wood A, Perry P, Danesh J. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. *Int J Epidemiol* 2010;**39**(5):1345-1359.

34. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991;**10**(7):1025-1035.

35. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ* 2007;**335**(7626):914-916.

36. Bell JA, Hamer M, van Hees VT, Singh-Manoux A, Kivimaki M, Sabia S. Healthy obesity and objective physical activity. *Am J Clin Nutr* 2015;**102**(2):268-275.

37. Ortega FB, Lee DC, Katzmarzyk PT, Ruiz JR, Sui X, Church TS, Blair SN. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J* 2013;**34**(5):389-397.

38. Hinnouho GM, Czernichow S, Dugravot A, Batty GD, Kivimaki M, Singh-Manoux A. Metabolically healthy obesity and risk of mortality: does the definition of metabolic health matter? *Diabetes Care* 2013;**36**(8):2294-2300.

39. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, Jordan HS, Kendall KA, Lux LJ, Mentor-Marcel R, Morgan LC, Trisolini MG, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014;**129**(25 Suppl 2):S102-S138.

40. National Institute for Health and Care Excellence. Obesity: Identification, assessment and management of overweight and obesity in children, young people and adults. National Clinical Guideline Centre; 2014 Nov.

41. Appleton SL, Seaborn CJ, Visvanathan R, Hill CL, Gill TK, Taylor AW, Adams RJ. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care* 2013;**36**(8):2388-2394.

42. Bobbioni-Harsch E, Pataky Z, Makoundou V, Laville M, Disse E, Anderwald C, Konrad T, Golay A. From metabolic normality to cardiometabolic risk factors in subjects with obesity. *Obesity (Silver Spring)* 2012;**20**(10):2063-2069.

43. Soriguer F, Gutierrez-Repiso C, Rubio-Martin E, Garcia-Fuentes E, Almaraz MC, Colomo N, Esteva dA, I, de Adana MS, Chaves FJ, Morcillo S, Valdes S, Rojo-Martinez G. Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study. *J Clin Endocrinol Metab* 2013;**98**(6):2318-2325.

44. den Engelsen C, Gorter KJ, Salome PL, Rutten GE. Development of metabolic syndrome components in adults with a healthy obese phenotype: a 3-year follow-up. *Obesity (Silver Spring)* 2013;**21**(5):1025-1030.

45. Bell JA, Hamer M, Sabia S, Singh-Manoux A, Batty GD, Kivimaki M. The natural course of healthy obesity over 20 years. *J Am Coll Cardiol* 2015;**65**(1):101-102.

46. Bell JA, Hamer M, Batty GD, Singh-Manoux A, Sabia S, Kivimaki M. Incidence of Metabolic Risk Factors Among Healthy Obese Adults: 20-Year Follow-Up. *J Am Coll Cardiol* 2015;**66**(7):871-873.

47. Guo F, Garvey WT. Cardiometabolic disease risk in metabolically healthy and unhealthy obesity: Stability of metabolic health status in adults. *Obesity (Silver Spring)* 2016;**24**(2):516-525.

48. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De BG, De BD, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**(11):987-1003.

49. Bell JA, Kivimaki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. *Obes Rev* 2014;**15**(6):504-515.

50. Gunter MJ, Xie X, Xue X, Kabat GC, Rohan TE, Wassertheil-Smoller S, Ho GY, Wylie-Rosett J, Greco T, Yu H, Beasley J, Strickler HD. Breast cancer risk in metabolically healthy but overweight postmenopausal women. *Cancer Res* 2015;**75**(2):270-274.

51. Murphy N, Cross AJ, Abubakar M, Jenab M, Aleksandrova K, Boutron-Ruault MC, Dossus L, Racine A, Kuhn T, Katzke VA, Tjonneland A, Petersen KE, Overvad K, Quiros JR, Jakszyn P, Molina-Montes E, Dorronsoro M, Huerta JM, Barricarte A, Khaw KT, Wareham N, Travis RC, Trichopoulou A, Lagiou P, Trichopoulos D, Masala G, Krogh V, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HB, Siersema PD, Peeters PH, Ohlsson B, Ericson U, Palmqvist R, Nystrom H, Weiderpass E, Skeie G, Freisling H, Kong SY, Tsilidis K, Muller DC, Riboli E, Gunter MJ. A Nested Case-Control Study of Metabolically Defined Body Size Phenotypes and Risk of Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS Med* 2016;**13**(4):e1001988.

52. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di AE, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;**375**(9733):2215-2222.

53. Cerhan JR, Moore SC, Jacobs EJ, Kitahara CM, Rosenberg PS, Adami HO, Ebbert JO, English DR, Gapstur SM, Giles GG, Horn-Ross PL, Park Y, Patel AV, Robien K, Weiderpass E, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Hartge P, Bernstein L, Berrington de GA. A pooled analysis of waist circumference and mortality in 650,000 adults. *Mayo Clin Proc* 2014;**89**(3):335-345.

54. Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. *J Am Coll Cardiol* 2013;**62**(10):921-925.

55. Neeland IJ, Turer AT, Ayers CR, Berry JD, Rohatgi A, Das SR, Khera A, Vega GL, McGuire DK, Grundy SM, de Lemos JA. Body fat distribution and incident cardiovascular disease in obese adults. *J Am Coll Cardiol* 2015;**65**(19):2150-2151.

56. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. *Br J Radiol* 2012;**85**(1009):1-10.

57. Smith SR, Stenlof KS, Greenway FL, McHutchison J, Schwartz SM, Dev VB, Berk ES, Kapikian R. Orlistat 60 mg reduces visceral adipose tissue: a 24-week randomized, placebo-controlled, multicenter trial. *Obesity (Silver Spring)* 2011;**19**(9):1796-1803.

58. Thomas EL, Makwana A, Newbould R, Rao AW, Gambarota G, Frost G, Delafont B, Mishra RG, Matthews PM, Berk ES, Schwartz SM, Bell JD, Beaver JD. Pragmatic study of orlistat 60 mg on abdominal obesity. *Eur J Clin Nutr* 2011;**65**(11):1256-1262.

59. Emdin CA, Khera AV, Natarajan P, Klarin D, Zekavat SM, Hsiao AJ, Kathiresan S. Genetic Association of Waist-to-Hip Ratio With Cardiometabolic Traits, Type 2 Diabetes, and Coronary Heart Disease. *JAMA* 2017;**317**(6):626-634.

60. Hagg S, Fall T, Ploner A, Magi R, Fischer K, Draisma HH, Kals M, de Vries PS, Dehghan A, Willems SM, Sarin AP, Kristiansson K, Nuotio ML, Havulinna AS, de Bruijn RF, Ikram MA, Kuningas M, Stricker BH, Franco OH, Benyamin B, Gieger C, Hall AS, Huikari V, Jula A, Jarvelin MR, Kaakinen M, Kaprio J, Kobl M, Mangino M, Nelson CP, Palotie A, Samani NJ, Spector TD, Strachan DP, Tobin MD, Whitfield JB, Uitterlinden AG, Salomaa V, Syvanen AC, Kuulasmaa K, Magnusson PK, Esko T, Hofman A, de Geus EJ, Lind L, Giedraitis V, Perola M, Evans A, Ferrieres J, Virtamo J, Kee F, Tregouet DA, Arveiler D, Amouyel P, Gianfagna F, Brambilla P, Ripatti S, van Duijn CM, Metspalu A, Prokopenko I, McCarthy MI, Pedersen NL, Ingelsson E. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. *Int J Epidemiol* 2015;**44**(2):578-586.

61. Nordestgaard BG, Palmer TM, Benn M, Zacho J, Tybjaerg-Hansen A, Davey SG, Timpson NJ. The effect of elevated body mass index on ischemic heart disease risk:

causal estimates from a Mendelian randomisation approach. *PLoS Med* 2012;**9**(5):e1001212.

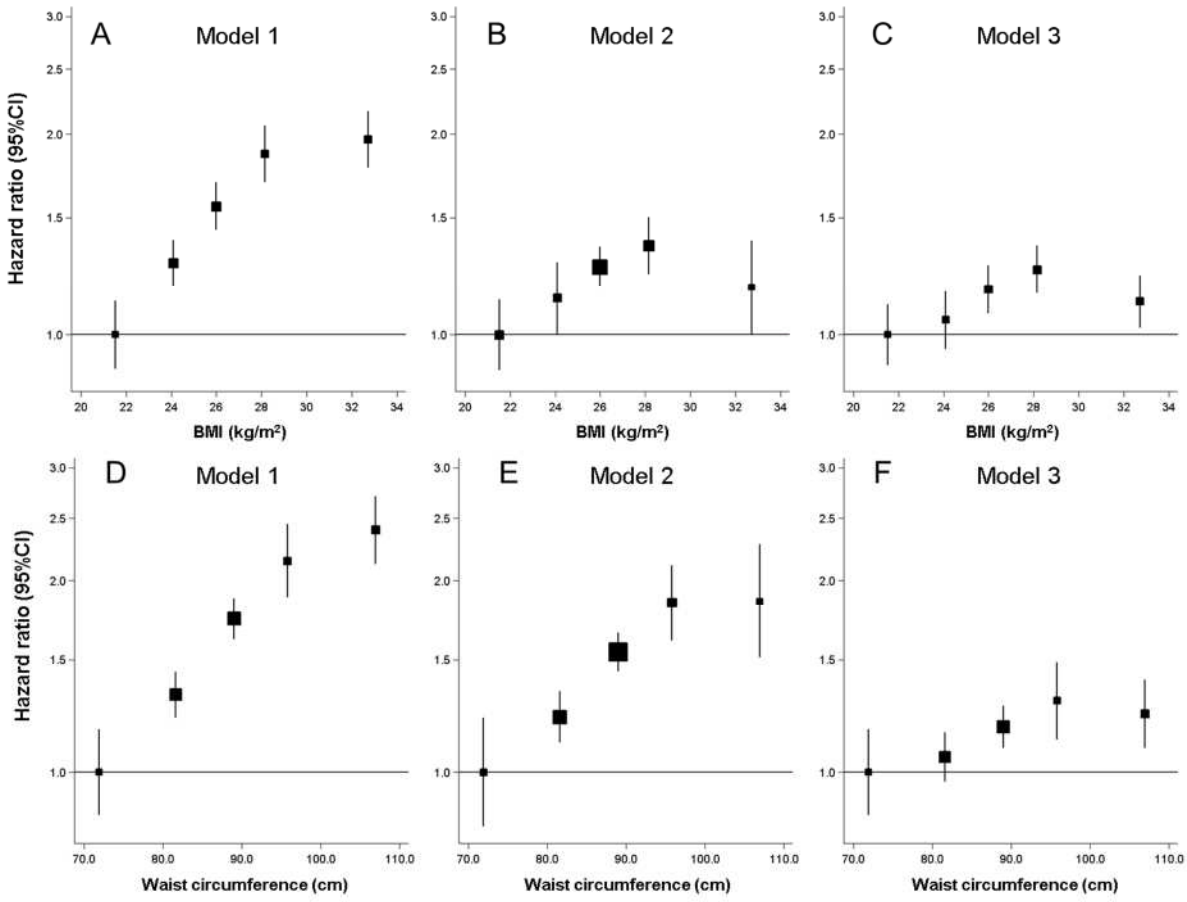
62. Holmes MV, Lange LA, Palmer T, Lanktree MB, North KE, Almoguera B, Buxbaum S, Chandrupatla HR, Elbers CC, Guo Y, Hoogeveen RC, Li J, Li YR, Swerdlow DI, Cushman M, Price TS, Curtis SP, Fornage M, Hakonarson H, Patel SR, Redline S, Siscovick DS, Tsai MY, Wilson JG, van der Schouw YT, FitzGerald GA, Hingorani AD, Casas JP, de Bakker PI, Rich SS, Schadt EE, Asselbergs FW, Reiner AP, Keating BJ. Causal effects of body mass index on cardiometabolic traits and events: a Mendelian randomization analysis. *Am J Hum Genet* 2014;**94**(2):198-208.

63. Kipnis V, Midthune D, Freedman L, Bingham S, Day NE, Riboli E, Ferrari P, Carroll RJ. Bias in dietary-report instruments and its implications for nutritional epidemiology. *Public Health Nutr* 2002;**5**(6A):915-923.

64. Rey-Lopez JP, de Rezende LF, Pastor-Valero M, Tess BH. The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. *Obes Rev* 2014;**15**(10):781-790.

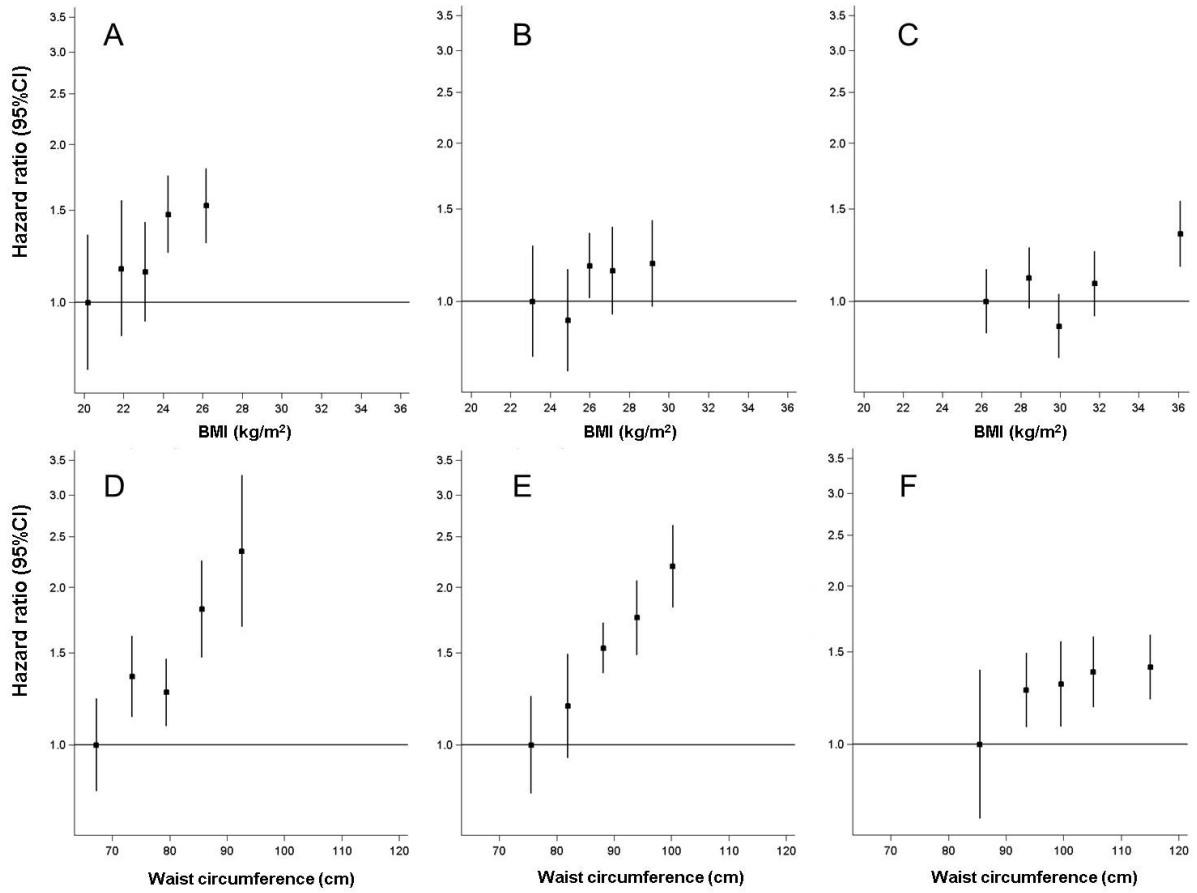
Figure Legends

Figure 1. Multivariate hazard ratios for coronary heart disease across quintiles of BMI (a,b,c) and waist circumference (d,e,f)



Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries and accompanied by a group-specific confidence interval (allowing a confidence interval to be attributed to the reference category). Age was used as the primary time variable, and analyses were stratified by sex and centre. n=17,733 (7,637 cases)
Model 1 (a and d). Adjusted for age, smoking, physical activity, Mediterranean diet score, energy and alcohol intake, educational level
Model 2. Model 1 + adjusted for WC (for BMI, b) or BMI (for WC, e)
Model 3 (c and f). Adjusted for age, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, history of diabetes
Abbreviations: BMI, body mass index; WC, waist circumference, CHD, coronary heart disease

Figure 2. Multivariate hazard ratios (HRs, Model 1 [a]) for CHD associated with quintiles of BMI per sex-specific tertile of WC (a,b,c) and quintiles of WC per sex-specific tertile of BMI (d,e,f)



[a] Country-specific HRs of CHD were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effect meta-analysis across 8 countries and accompanied by a group-specific confidence interval (allowing a confidence interval to be attributed to the reference category). Age was used as the primary time variable, and analyses were stratified by sex and centre. n=17,733 (7,637 cases)

Model 1: Adjusted for age at baseline, smoking, physical activity, educational level, Mediterranean diet score, energy and alcohol intake

HRs for quintiles of BMI, in the first (a), second (b) and third (c) sex-specific tertile of WC

Boundaries (cm) by tertiles: Tertile 1, 59-91(M), 54-76(F); Tertile 2, 92-99(M),77-86(F); Tertile 3, 100-151(M), 87-137(F) .

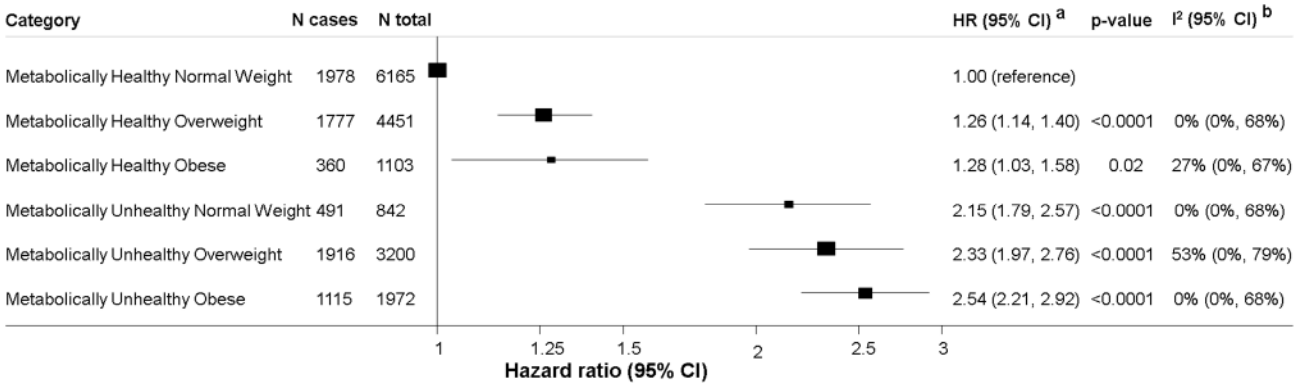
HRs for quintiles of WC, in the first (d), second (e) and third (f) sex-specific tertile of BMI

Boundaries (kg/m^2) by tertiles: Tertile 1, 18.5-25.1(M), 18.5-23.8(F); Tertile 2, 25.1-27.9(M),23.8-27.4; Tertile 3, 27.9-49.4(M), 27.4-62.5(F).

P for interaction between BMI and WC = 0.005

Abbreviations: BMI, body mass index; WC, waist circumference; CHD, coronary heart disease

Figure 3. Multivariate hazard ratios of CHD in metabolically-defined body size phenotypes.



[a] Country-specific HRs of CHD were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries. Age was used as the underlying time scale, analyses were stratified by sex and centre, HRs adjusted for age, smoking, educational level, physical activity, Mediterranean diet score, energy and alcohol intake (Model B). n=17,733 participants (7,637 CHD cases). P for interaction between BMI and MetS = 0.19.

[b] Heterogeneity across 8 European countries

Table 1. Baseline characteristics [a] of subcohort participants across metabolically defined body size phenotypes

	Normal weight		Overweight		Obese				
	Metabolically healthy normal weight	**Metabolically unhealthy normal weight**	**Metabolically healthy overweight**	**Metabolically unhealthy overweigh**	**Metabolically healthy obese**	**Metabolically unhealthy obese**	***p* Healthy vs unhealthy obese [b]**	***p* Healthy obese vs normal weight [b]**	**Unadjusted mean [c]**
N	4282	368	2761	1403	751	909			
Women (%)	69 (67, 71)	69 (64, 73)	55 (53, 57)	51 (48, 53)	64 (61, 67)	59 (56, 62)	0.01	0.01	63
Age (years)	50.8 (50.6, 51.1)	55.5 (54.7, 56.3)	52.3 (51.9, 52.6)	54.8 (54.4, 55.3)	52.8 (52.2, 53.4)	54.4 (53.9, 54.9)	<.0001	<.0001	53.6 (9.3)
BMI (kg/m2)	22.7 (22.6, 22.7)	23.5 (23.3, 23.7)	26.9 (26.9, 27.0)	27.5 (27.4, 27.6)	32.6 (32.5, 32.8)	33.3 (33.2, 33.5)	<.0001	NR	26.1 (4.1)
WC (cm)[d]	79.9 (79.7, 80.1)	85.5 (84.9, 86.2)	88.9 (88.7, 89.2)	93.1 (92.8, 93.5)	101.2 (100.8, 101.7)	105.2 (104.7, 105.6)	NR	NR	86.3 (12.6)
Glucose (mmol/l) [d,e]	4.78 (4.73, 4.83)	5.39 (5.24, 5.54)	4.80 (4.75, 4.86)	5.39 (5.31, 5.47)	4.83 (4.72, 4.93)	5.84 (5.74, 5.94)	NR	0.40	5.04 (1.59)
HbA1c (%)	5.45 (5.43, 5.47)	5.62 (5.56, 5.68)	5.47 (5.45, 5.50)	5.69 (5.66, 5.72)	5.57 (5.52, 5.61)	5.96 (5.92, 6.00)	<.0001	<.0001	5.5 (0.6)
SBP (mmHg) [d]	127.7 (127.1, 128.3)	137.6 (135.8, 139.3)	131.5 (130.8, 132.2)	139.0 (138.1, 139.9)	135.5 (134.2, 136.7)	143.2 (142.0, 144.3)	NR	<.0001	132.9 (19.7)
DBP (mm Hg) [d]	78.9 (78.5, 79.2)	84.0 (83.0, 85.0)	81.6 (81.2, 81.9)	85.5 (84.9, 86.0)	84.4 (83.7, 85.1)	87.9 (87.2, 88.6)	NR	<.0001	82 (10.7)
HDL, chol (mmol/l) [d,e]	1.60 (1.58, 1.61)	1.17 (1.13, 1.20)	1.48 (1.47, 1.50)	1.15 (1.13, 1.16)	1.46 (1.43, 1.48)	1.10 (1.08, 1.13)	NR	<.0001	1.48 (0.42)
Total chol (mmol/L) [e]	5.82 (5.78, 5.86)	6.35 (6.24, 6.46)	5.99 (5.95, 6.04)	6.33 (6.27, 6.39)	5.94 (5.87, 6.02)	6.23 (6.15, 6.30)	<.0001	0.004	6.01 (1.13)
Non HDL, chol (mmol/l) [e]	4.22 (4.18, 4.26)	5.18 (5.07, 5.30)	4.51 (4.47, 4.55)	5.19 (5.13, 5.25)	4.49 (4.41, 4.57)	5.12 (5.05, 5.20)	<.0001	<.0001	4.53 (1.18)
CRP (mg/L)	1.58 (1.43, 1.73)	2.06 (1.63, 2.49)	2.20 (2.03, 2.37)	2.63 (2.40, 2.86)	3.74 (3.44, 4.05)	4.39 (4.11, 4.67)	0.001	<.0001	2.34 (4.23)
Triglycerides (mmol/l) [d, e]	1.13 (1.10, 1.15)	2.25 (2.17, 2.33)	1.22 (1.19, 1.25)	2.25 (2.20, 2.29)	1.22 (1.16, 1.27)	2.31 (2.25, 2.36)	NR	0.003	1.41 (0.93)
Vegetables (portions/d) [f]	2.67 (2.62, 2.71)	2.65 (2.52, 2.78)	2.68 (2.63, 2.73)	2.73 (2.66, 2.80)	2.60 (2.51, 2.70)	2.71 (2.62, 2.80)	0.08	0.19	2.54 (1.81)
Fruit (portions/d) [g]	2.92 (2.85, 2.99)	2.94 (2.73, 3.15)	3.09 (3.01, 3.17)	3.07 (2.96, 3.18)	3.03 (2.88, 3.18)	3.16 (3.03, 3.30)	0.17	0.19	3.02 (2.29)
Red meat (portions/d) [h]	1.03 (1.01, 1.05)	1.09 (1.03, 1.15)	1.12 (1.10, 1.14)	1.14 (1.11, 1.17)	1.15 (1.11, 1.19)	1.21 (1.17, 1.24)	0.05	<.0001	1.09 (0.74)
Mediterranean diet score	8.84 (8.77, 8.92)	8.64 (8.42, 8.86)	8.75 (8.66, 8.83)	8.76 (8.65, 8.88)	8.72 (8.57, 8.88)	8.59 (8.45, 8.74)	0.21	0.16	8.55 (3.08)
Energy intake (kcal/day)	2201 (2181, 2220)	2186 (2128, 2243)	2202 (2180, 2224)	2196 (2165, 2226)	2240 (2199, 2280)	2228 (2191, 2265)	0.67	0.08	2149 (623)
Alcohol (drinks/d) [i]	1.85 (1.78, 1.91)	1.82 (1.62, 2.01)	1.84 (1.76, 1.92)	1.82 (1.72, 1.93)	1.78 (1.64, 1.92)	1.72 (1.59, 1.85)	0.56	0.36	1.62 (2.13)
Physical activity (%)									
Inactive	22 (21, 24)	25 (21, 29)	23 (22, 25)	27 (25, 29)	31 (28, 34)	32 (29, 34)	0.71	<.0001	23
Moderately inactive	34 (32, 35)	39 (35, 44)	34 (32, 36)	36 (33, 38)	29 (26, 33)	34 (31, 37)	0.04	0.02	33
Moderately active	24 (23, 25)	19 (14, 23)	22 (21, 24)	19 (17, 22)	20 (17, 23)	18 (16, 21)	0.37	0.02	22
Active	20 (19, 22)	16 (12, 21)	20 (19, 22)	17 (15, 20)	19 (17, 22)	16 (13, 19)	0.07	0.63	21
Education (%)									
No schooling / Primary	35 (33, 36)	43 (39, 48)	43 (41, 44)	46 (44, 48)	52 (49, 55)	51 (48, 54)	0.65	<.0001	38
Secondary	15 (14, 16)	12 (09, 16)	14 (12, 15)	11 (09, 13)	11 (08, 13)	10 (07, 12)	0.44	0.002	15
Vocational/University	50 (48, 51)	44 (40, 49)	44 (42, 46)	43 (40, 45)	37 (34, 41)	40 (37, 43)	0.31	<.0001	47
Smoking status (%)									
Never	42 (40, 44)	38 (33, 43)	45 (44, 47)	41 (38, 43)	46 (42, 49)	44 (41, 48)	0.54	0.04	45
Former	29 (27, 30)	24 (20, 29)	31 (29, 33)	33 (30, 35)	34 (31, 38)	32 (29, 35)	0.36	0.002	29
Current	30 (28, 31)	38 (34, 42)	24 (22, 25)	27 (24, 29)	20 (17, 23)	23 (20, 26)	0.10	<.0001	26

[a] Values are adjusted means or percentages (and confidence interval) from ANCOVA , adjusted for centre, sex, age, education, and smoking, as well as energy intake for dietary variables.
[b] P-values were calculated using F-test
[c] Unadjusted means (SD) or percentages overall in the subcohort (n =10,474)
[d] Values in bold are components of the metabolic syndrome. The test for difference between metabolically healthy and unhealthy is not presented for these variables as it is not relevant (NR).
[e] Conversion factors from mmol/L to mg/dL: glucose x18.02; cholesterol x38.67; triglycerides x88.57
[f] 1 vegetable portion = 80g
[g] 1 fruit portion = 80g
[h] 1 red meat portion = 110g of unprocessed meat and 50g of processed meat
[i] 1 alcoholic drink corresponds to 10g of ethanol
Abbreviations: BMI, body mass index; WC, waist circumference; chol, cholesterol; CRP, C-reactive protein; NR, not relevant

Table 2. Multivariate hazard ratios for coronary heart disease associated with body mass index and waist circumference

	HR[a]	95% CI	p-value	I^{2} [b]	95% CI
Model 0 [c]					
BMI (kg/m^2)	1.27	(1.21, 1.33)	<.0001	44%	(0%, 75%)
Waist circumference (cm)	1.34	(1.26, 1.42)	<.0001	47%	(0%, 76%)
Model 1 [d]					
BMI (kg/m^2)	1.25	(1.19, 1.32)	<.0001	46%	(0%, 76%)
Waist circumference (cm)	1.32	(1.24, 1.41)	<.0001	51%	(0%, 78%)
Model 2 [e]					
BMI (kg/m^2)	1.06	(0.97, 1.15)	0.20	19%	(0%, 62%)
Waist circumference (cm)	1.24	(1.10, 1.40)	<.0001	43%	(0%, 75%)
Model 3 [f]					
BMI (kg/m^2)	1.05	(1.01, 1.10)	0.03	0%	(0%, 68%)
Waist circumference (cm)	1.06	(1.00, 1.13)	0.06	34%	(0%, 71%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries. HRs are expressed per 1 SD increase of anthropometric marker (BMI: 4.10kg/m^2, WC: 12.7cm), with age as the primary time variable, stratified by sex and centre. n=17,733 (7,637 cases)

[b] Heterogeneity across 8 European countries.

[c] Model 0. HR adjusted for age and smoking

[d] Model 1. HR adjusted for age, smoking, physical activity, Mediterranean diet score, energy and alcohol intake, educational level

[e] Model 2. Model 1 + waist circumference (for BMI) or BMI (for waist circumference)

[f] Model 3. HR adjusted for age, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, history of diabetes

Abbreviations: BMI, body mass index; CHD, coronary heart disease

Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis

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Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis

Table S1. Baseline characteristics [a] and metabolic health status in members of the subcohort, by country

	Denmark	Greece	Germany	Italy	Netherlands	Spain	Sweden	United Kingdom
N	1895	1124	1356	1800	1270	550	1481	998
Age (years)	56.6 (4.4)	52.2 (12.2)	50 (8.7)	50.3 (7.9)	52.7 (10.7)	50.6 (8.4)	57.6 (7.7)	57 (10.7)
Women (%)	46.7	61.7	60.5	66.3	83.9	68.0	61.7	60.6
MetS (%)	27.3	28.1	29.3	22.1	24.1	26.6	25.7	22.1
Normal weight (%)	43.8	27.9	45.6	45.7	51.8	23.3	51.7	51.5
Overweight (%)	42.6	42.0	39.3	39.4	36.4	46.9	37.0	37.5
Obese (%)	13.7	30.1	15.1	14.8	11.8	29.8	11.3	11.0
MHO (% of the obese)	38.6	55.0	31.7	46.8	48.7	57.9	37.1	40.9

[a] Values are unadjusted means (SD) or percentages.

n= 10,474 members of the subcohort included in the analytical sample

Abbreviations: MHO, metabolically healthy obese; MetS, metabolic syndrome

Table S2. Sensitivity analysis: HR for CHD in different complete-case samples specific to each analysis.

		HR [a]	95% CI	p	N cases	N total	I^{2} [b]	95% CI
BMI and Waist Circumference								
Model 1 [c]								
BMI		1.24	(1.17, 1.30)	<.0001	9212	23634	55%	(6%, 79%)
Waist circumference		1.31	(1.24, 1.38)	<.0001	9212	23634	47%	(0%, 76%)
Model 2 [d]								
BMI		1.05	(0.97, 1.14)	0.23	9212	23634	33%	(0%, 69%)
Waist circumference		1.24	(1.12, 1.37)	<.0001	9212	23634	40%	(0%, 73%)
Model 3 [e]								
BMI		1.06	(1.01, 1.10)	0.01	8319	18700	6%	(0%, 68%)
Waist circumference		1.07	(1.01, 1.14)	0.01	8319	18700	21%	(0%, 63%)
Metabolically-defined body size phenotypes								
Model B [f]								
BMI	MetS							
Normal weight	Metabolically Healthy	1.00	(ref)		2833	7664		
Overweight	Metabolically Healthy	1.26	(1.15, 1.38)	<.0001	2513	6748	0%	(0%, 68%)
Obese	Metabolically Healthy	1.41	(1.15, 1.72)	<.0001	687	2159	47%	(0%, 77%)
Normal weight	Metabolically Unhealthy	1.98	(1.67, 2.35)	<.0001	530	929	0%	(0%, 68%)
Overweight	Metabolically Unhealthy	2.26	(1.90, 2.67)	<.0001	2172	3703	63%	(19%, 83%)
Obese	Metabolically Unhealthy	2.44	(2.11, 2.82)	<.0001	1356	2495	4%	(0%, 69%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effect meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and centre.

[b] Heterogeneity across 8 European countries.

[c] Model 1. HRs adjusted for age, smoking, physical activity, Mediterranean diet score, energy and alcohol intake, educational level

[d] Model 2. Model 1 + waist circumference (for BMI) or BMI (for waist circumference)

[e] Model 3. HRs adjusted for age, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, history of diabetes

[f] Model B. HRs adjusted for age, smoking, educational level, physical activity, Mediterranean diet score, energy and alcohol intake

Table S3. Sensitivity analysis: HR for CHD where missing values are imputed by multiple imputation

		HR [a]	95% CI	p
BMI and Waist Circumference				
Model 1 [b]				
BMI		1.28	(1.24, 1.33)	<.0001
Waist circumference		1.32	(1.27, 1.39)	<.0001
Model 2 [c]				
BMI		1.16	(1.07, 1.24)	<.0001
Waist circumference		1.15	(1.05, 1.25)	0.002
Model 3 [d]				
BMI		1.11	(1.06, 1.16)	<.0001
Waist circumference		1.10	(1.04, 1.16)	<.0001
Metabolically-defined body size phenotypes				
Model B [e]				
BMI	MetS			
Normal weight	Metabolically Healthy	1.00	(ref)	
Overweight	Metabolically Healthy	1.35	(1.20, 1.52)	<.0001
Obese	Metabolically Healthy	1.67	(1.39, 1.99)	<.0001
Normal weight	Metabolically Unhealthy	1.78	(1.46, 2.18)	<.0001
Overweight	Metabolically Unhealthy	2.22	(1.98, 2.49)	<.0001
Obese	Metabolically Unhealthy	2.43	(2.09, 2.81)	<.0001

[a] HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. Age was used as the underlying time scale, models were stratified by sex and centre. N=25,653 (12,240 cases). 5 imputed datasets, results combined by Rubin's rules.

[b] Model 1. HRs adjusted for age, smoking, physical activity, Mediterranean diet score, energy and alcohol intake, educational level

[c] Model 2. Model 1 + waist circumference (for BMI) or BMI (for waist circumference)

[d] Model 3. HRs adjusted for age, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, history of diabetes

[e] Model B. HRs adjusted for age, smoking, physical activity, Mediterranean diet score, energy and alcohol intake, educational level

Table S4. Sensitivity analysis: HR for CHD after exclusion of first two years of follow-up across metabolically-defined body size phenotypes

BMI	MetS	HR [a]	95%CI	p-value	N cases	N total	I^{2} [b]	95% CI
Model A [c]								
Normal weight	Metabolically Healthy	1.00	(ref)		1802	5961		
Overweight	Metabolically Healthy	1.22	(1.10, 1.35)	<.0001	1581	4241	0%	(0%, 68%)
Obese	Metabolically Healthy	1.24	(0.99, 1.57)	0.07	323	1059	37%	(0%, 72%)
Normal weight	Metabolically Unhealthy	2.12	(1.74, 2.58)	<.0001	428	778	0%	(0%, 68%)
Overweight	Metabolically Unhealthy	2.30	(1.96, 2.72)	<.0001	1678	2946	50%	(0%, 78%)
Obese	Metabolically Unhealthy	2.54	(2.23, 2.91)	<.0001	976	1829	0%	(0%, 68%)
Model B [d]								
Normal weight	Metabolically Healthy	1.00	(ref)		1802	5961		
Overweight	Metabolically Healthy	1.23	(1.11, 1.37)	<.0001	1581	4241	0%	(0%, 68%)
Obese	Metabolically Healthy	1.25	(0.99, 1.58)	0.06	323	1059	35%	(0%, 71%)
Normal weight	Metabolically Unhealthy	2.09	(1.72, 2.54)	<.0001	428	778	0%	(0%, 68%)
Overweight	Metabolically Unhealthy	2.29	(1.90, 2.75)	<.0001	1678	2946	58%	(7%, 81%)
Obese	Metabolically Unhealthy	2.46	(2.14, 2.82)	<.0001	976	1829	0%	(0%, 68%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and centre. n=16,814 (6,788 CHD cases).
[b] Heterogeneity across 8 European countries
[c] Model A. HRs adjusted for age, smoking, educational level.
[d] Model B included the same variables as model A + physical activity, Mediterranean diet score, energy and alcohol intake

Table S5. Sensitivity analysis: HR for hard CHD (myocardial infarction) across metabolically-defined body size phenotypes

BMI	MetS	HR [a]	95%CI	p-value	N cases	N total	I^2 [b]	95% CI
Model A[c]								
Normal weight	Metabolically Healthy	1.00	(ref)		1303	6165		
Overweight	Metabolically Healthy	1.23	(1.07, 1.41)	0.003	1144	4451	0%	(0%, 68%)
Obese	Metabolically Healthy	1.32	(1.01, 1.73)	0.045	234	1103	43%	(0%, 75%)
Normal weight	Metabolically Unhealthy	2.13	(1.70, 2.67)	<.0001	325	842	12%	(0%, 71%)
Overweight	Metabolically Unhealthy	2.21	(1.92, 2.55)	<.0001	1283	3200	19%	(0%, 62%)
Obese	Metabolically Unhealthy	2.57	(2.17, 3.04)	<.0001	773	1972	12%	(0%, 72%)
Model B [d]								
Normal weight	Metabolically Healthy	1.00	(ref)		1303	6165		
Overweight	Metabolically Healthy	1.24	(1.08, 1.43)	0.002	1144	4451	3%	(0%, 69%)
Obese	Metabolically Healthy	1.30	(1.00, 1.70)	0.049	234	1103	39%	(0%, 73%)
Normal weight	Metabolically Unhealthy	2.10	(1.71, 2.58)	<.0001	325	842	0%	(0%, 68%)
Overweight	Metabolically Unhealthy	2.21	(1.89, 2.57)	<.0001	1283	3200	26%	(0%, 67%)
Obese	Metabolically Unhealthy	2.46	(2.10, 2.90)	<.0001	773	1972	1%	(0%, 68%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and centre. n=17,733 participants (5,062 CHD cases)
[b] Heterogeneity across 8 European countries
[c] Model A. HRs adjusted for age, smoking, educational level.
[d] Model B included the same variables as model A + physical activity, Mediterranean diet score, energy and alcohol intake

Table S6. Sensitivity analysis: HR for CHD events across metabolically-defined body size phenotypes in non-smokers only

BMI	MetS	HR [a]	95%CI	p-value	N cases	N total	I^{2} [b]	95% CI
Model A [c]								
Normal weight	Metabolically Healthy	1.00	(ref)		1193	4166		
Overweight	Metabolically Healthy	1.22	(1.04, 1.38)	0.003	1173	3215	0%	(0%,68%)
Obese	Metabolically Healthy	1.26	(0.96, 1.67)	0.10	272	871	45%	(0%,76%)
Normal weight	Metabolically Unhealthy	2.15	(1.72, 2.69)	<.0001	277	506	0%	(0%,68%)
Overweight	Metabolically Unhealthy	2.32	(2.00, 2.70)	<.0001	1233	2193	7%	(0%,70%)
Obese	Metabolically Unhealthy	2.59	(2.21, 3.03)	<.0001	763	1443	0%	(0%,68%)
Model B[d]								
Normal weight	Metabolically Healthy	1.00	(ref)		1193	4166		
Overweight	Metabolically Healthy	1.23	(1.08,1.40)	0.002	1173	3215	47%	(0%, 80%)
Obese	Metabolically Healthy	1.29	(0.99,1.67)	0.06	272	871	0%	(0%, 79%)
Normal weight	Metabolically Unhealthy	2.15	(1.71,2.71)	<.0001	277	506	35%	(0%, 75%)
Overweight	Metabolically Unhealthy	2.32	(1.97,2.73)	<.0001	1233	2193	44%	(0%, 80%)
Obese	Metabolically Unhealthy	2.58	(2.18,3.04)	<.0001	763	1443	0%	(0%, 79%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and centre. n=12,394 (4,911 cases)

[b] Heterogeneity across 8 European countries

[c] Model A. HRs age, smoking (never, former), educational level.

[d] Model B included the same variables as model A + physical activity, Mediterranean diet score, energy and alcohol intake

Table S7. Sensitivity analysis: HR for CHD events with the highest level of certainty across metabolically-defined body size phenotypes

BMI	MetS	HR [a]	95%CI	p-value	N cases	N total	I^2 [b]	95% CI
Model A [c]								
Normal weight	Metabolically Healthy	1.00	(ref)		268	3159		
Overweight	Metabolically Healthy	1.39	(1.04, 1.86)	0.03	325	2598	40%	(0%, 78%)
Obese	Metabolically Healthy	1.11	(0.79, 1.55)	0.55	65	738	0%	(0%, 79%)
Normal weight	Metabolically Unhealthy	2.58	(1.68, 3.95)	<.0001	75	374	21%	(0%, 66%)
Overweight	Metabolically Unhealthy	2.78	(2.17, 3.57)	<.0001	389	1707	3%	(0%, 80%)
Obese	Metabolically Unhealthy	2.99	(2.36, 3.79)	<.0001	262	1218	0%	(0%, 79%)
Model B[d]								
Normal weight	Metabolically Healthy	1.00	(ref)		268	3159		
Overweight	Metabolically Healthy	1.44	(1.05, 1.99)	0.03	325	2598	47%	(0%, 80%)
Obese	Metabolically Healthy	1.13	(0.81, 1.59)	0.47	65	738	0%	(0%, 79%)
Normal weight	Metabolically Unhealthy	2.79	(1.73, 4.49)	<.0001	75	374	35%	(0%, 75%)
Overweight	Metabolically Unhealthy	2.88	(2.09, 3.98)	<.0001	389	1707	44%	(0%, 80%)
Obese	Metabolically Unhealthy	2.93	(2.29, 3.77)	<.0001	262	1218	0%	(0%, 79%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and centre. n=9,794 (1,384 cases)

[b] Heterogeneity across 8 European countries

[c] Model A. HRs adjusted for age, smoking, educational level.

[d] Model B included the same variables as model A + physical activity, Mediterranean diet score, energy and alcohol intake

Table S8. Sensitivity analysis: HR for CHD across metabolically-defined body size phenotypes separately for men and women

BMI	MetS	HR [a]	95%CI	p-value	N cases	N total	I^{2} [b]	95% CI
Men								
Normal weight	Metabolically Healthy	1.00	(ref)		1053	2310		
Overweight	Metabolically Healthy	1.32	(1.16, 1.51)	<.0001	1168	2328	0%	(0%,68%)
Obese	Metabolically Healthy	1.28	(0.99, 1.65)	0.06	184	415	7%	(0%,70%)
Normal weight	Metabolically Unhealthy	2.53	(1.90, 3.37)	<.0001	243	346	45%	(0%,76%)
Overweight	Metabolically Unhealthy	2.35	(2.03, 2.73)	<.0001	1239	1861	25%	(0%,66%)
Obese	Metabolically Unhealthy	2.47	(2.06, 2.95)	<.0001	622	954	0%	(0%,68%)
Women								
Normal weight	Metabolically Healthy	1.00	(ref)		925	3855		
Overweight	Metabolically Healthy	1.19	(1.03, 1.38)	0.02	609	2123	0%	(0%,68%)
Obese	Metabolically Healthy	1.28	(1.02, 1.60)	0.03	176	688	0%	(0%,68%)
Normal weight	Metabolically Unhealthy	1.85	(1.48, 2.31)	<.0001	248	496	0%	(0%,68%)
Overweight	Metabolically Unhealthy	2.36	(2.01, 2.76)	<.0001	677	1339	26%	(0%,67%)
Obese	Metabolically Unhealthy	2.72	(2.27, 3.26)	<.0001	493	1018	30%	(0%,69%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and centre. n=8,214 men (4,509 cases) and n=9,519 (n=3,128 cases).
HRs adjusted for age, smoking (never, former), educational level, physical activity, Mediterranean diet score, energy and alcohol intake
[b] Heterogeneity across 8 European countries

Table S9. Sensitivity analysis: HR for CHD in metabolically-defined body size phenotypes where the definition of MetS does not include the waist circumference criterion

BMI	MetS without WC	HR [a]	95%CI	p-value	N cases	N total	I^2 [b]	95% CI
Model A [c]								
Normal weight	Metabolically Healthy	1.00	(ref)		1458	5166		
Overweight	Metabolically Healthy	1.36	(1.20, 1.56)	<.0001	1532	3999	6%	(0%, 69%)
Obese	Metabolically Healthy	1.43	(1.13, 1.81)	0.003	357	1095	42%	(0%, 74%)
Normal weight	Metabolically Unhealthy	2.01	(1.72, 2.35)	<.0001	1011	1841	19%	(0%, 62%)
Overweight	Metabolically Unhealthy	2.52	(2.17, 2.94)	<.0001	2161	3652	41%	(0%, 74%)
Obese	Metabolically Unhealthy	2.92	(2.54, 3.34)	<.0001	1118	1980	0%	(0%, 68%)
Model B [d]								
Normal weight	Metabolically Healthy	1.00	(ref)		1458	5166		
Overweight	Metabolically Healthy	1.38	(1.20, 1.57)	<.0001	1532	3999	7%	(0%, 70%)
Obese	Metabolically Healthy	1.43	(1.14, 1.81)	0.002	357	1095	39%	(0%, 73%)
Normal weight	Metabolically Unhealthy	2.00	(1.72, 2.32)	<.0001	1011	1841	8%	(0%, 70%)
Overweight	Metabolically Unhealthy	2.49	(2.11, 2.94)	<.0001	2161	3652	48%	(0%, 77%)
Obese	Metabolically Unhealthy	2.82	(2.45, 3.25)	<.0001	1118	1980	0%	(0%, 68%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effect meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and centre. n=17,733 participants (7,637 CHD cases)

[b] Heterogeneity across 8 European countries

[c] Model A. HRs adjusted for age, smoking, educational level.

[d] Model B included the same variables as model A + physical activity, Mediterranean diet score, energy and alcohol intake

Table S10. Sensitivity analysis: HR for CHD in metabolically-defined body size phenotypes where "metabolically healthy" is defined as having none of the 4 abnormalities

BMI	Healthy defined as having 0 abnormality	HR [a]	95%CI	p-value	N cases	N total	I^{2} [b]	95% CI
Model A [c]								
Normal weight	Metabolically Healthy	1.00	(ref)		390	2148		
Overweight	Metabolically Healthy	1.24	(0.99, 1.56)	0.06	260	1040	0%	(0%, 68%)
Obese	Metabolically Healthy	1.15	(0.72, 1.84)	0.55	36	198	0%	(0%, 68%)
Normal weight	Metabolically Unhealthy	1.93	(1.62, 2.31)	<.0001	2079	4859	0%	(0%, 68%)
Overweight	Metabolically Unhealthy	2.67	(2.29, 3.12)	<.0001	3433	6611	0%	(0%, 68%)
Obese	Metabolically Unhealthy	3.19	(2.64, 3.85)	<.0001	1439	2877	0%	(0%, 68%)
Model B [d]								
Normal weight	Metabolically healthy	1.00	(ref)		390	2148		
Overweight	Metabolically Healthy	1.24	(0.99, 1.56)	0.06	260	1040	0%	(0%, 68%)
Obese	Metabolically Healthy	1.21	(0.76, 1.92)	0.43	36	198	0%	(0%, 68%)
Normal weight	Metabolically Unhealthy	1.94	(1.62, 2.32)	<.0001	2079	4859	0%	(0%, 68%)
Overweight	Metabolically Unhealthy	2.68	(2.28, 3.14)	<.0001	3433	6611	0%	(0%, 68%)
Obese	Metabolically Unhealthy	3.12	(2.57, 3.80)	<.0001	1439	2877	2%	(0%, 68%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effects meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and centre. n=17,733 participants (7,637 CHD cases)
[b] Heterogeneity across 8 European countries
[c] Model A. HRs adjusted for age, smoking, educational level.
[d] Model B included the same variables as model A + physical activity, Mediterranean diet score, energy and alcohol intake

Table S11. Sensitivity analysis: HR for CHD in metabolically-defined body size phenotypes where obesity is defined by WC, and MetS does not include criteria on WC

WC	MetS without WC	HR [a]	95%CI	p-value	N cases	N total	I^2 [b]	95% CI
Model A [c]								
Normal WC [d]	Metabolically Healthy	1.00	(ref)		1653	5707		
Overweight [e]	Metabolically Healthy	1.40	(1.15, 1.69)	0.001	1031	2729	55%	(0%, 80%)
Obese [f]	Metabolically Healthy	1.37	(1.11, 1.69)	0.003	663	1824	50%	(0%, 78%)
Normal WC [d]	Metabolically Unhealthy	1.96	(1.70, 2.25)	<.0001	1143	2075	0%	(0%, 68%)
Overweight [e]	Metabolically Unhealthy	2.43	(2.09, 2.82)	<.0001	1340	2292	20%	(0%, 62%)
Obese [f]	Metabolically Unhealthy	2.92	(2.47, 3.45)	<.0001	1807	3106	47%	(0%, 76%)
Model B [g]								
Normal WC [d]	Metabolically Healthy	1.00	(ref)		1653	5707		
Overweight [e]	Metabolically Healthy	1.41	(1.17, 1.70)	<.0001	1031	2729	53%	(0%, 79%)
Obese [f]	Metabolically Healthy	1.39	(1.12, 1.73)	0.003	663	1824	51%	(0%, 78%)
Normal WC [d]	Metabolically Unhealthy	1.94	(1.68, 2.24)	<.0001	1143	2075	0%	(0%, 68%)
Overweight [e]	Metabolically Unhealthy	2.43	(2.09, 2.84)	<.0001	1340	2292	24%	(0%, 65%)
Obese [f]	Metabolically Unhealthy	2.84	(2.38, 3.39)	<.0001	1807	3106	50%	(0%, 77%)
Model C [h]								
Normal WC [d]	Metabolically Healthy	1.00	(ref)		1653	5707		
Overweight [e]	Metabolically Healthy	1.33	(1.10, 1.60)	<.0001	1031	2729	44%	(0%, 75%)
Obese [f]	Metabolically Healthy	1.22	(0.99, 1.51)	0.06	663	1824	25%	(0%, 66%)
Normal WC [d]	Metabolically Unhealthy	1.93	(1.66, 2.24)	<.0001	1143	2075	0%	(0%, 68%)
Overweight [e]	Metabolically Unhealthy	2.26	(1.92, 2.66)	<.0001	1340	2292	21%	(0%, 63%)
Obese [f]	Metabolically Unhealthy	2.44	(1.99, 2.99)	<.0001	1807	3106	25%	(0%, 66%)

[a] Country-specific HRs were estimated from Prentice-weighted Cox proportional hazards models, and 95%CI estimated with robust variance, to take into account the case-cohort design. HRs were combined by multivariate random-effect meta-analysis across 8 countries. Age was used as the underlying time scale, models were stratified by sex and EPIC study centre. n=17,733 participants (7,637 CHD cases); [b] Heterogeneity across 8 countries;
[c] Model A. HRs adjusted for age, smoking, educational level.;
[d] Normal WC: WC<94 for men, 80 for women; [e] Overweight: 94≤WC<102 for men, 80≤WC<88 for women; [f] Obese: WC≥102 for men, 88 for women
[g] Model B included the same variables as model A + physical activity, Mediterranean diet score, energy and alcohol intake
[h] Model C included the same variables as model B + BMI

Table S12. Cross-classification in metabolically-defined body size phenotypes where body size is defined by BMI or by WC

BMI-defined	WC-defined						
	MHANW	MUANW	MHAOW	MUAOW	MHAO	MUAO	Total
MHNW	4447	999	648	0	71	0	6165
MUNW	0	394	0	391	0	57	842
MHOW	1246	452	1905	0	848	0	4451
MUOW	0	218	0	1753	0	1229	3200
MHO	14	8	176	0	905	0	1103
MUO	0	4	0	148	0	1820	1972
Total	5707	2075	2729	2292	1824	3106	17733

Abbreviations: MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy normal weight; MHOW, metabolically healthy overweight; MUOW, metabolically unhealthy overweight; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; MHANW, metabolically healthy abdominally normal weight; MUANW, metabolically unhealthy abdominally normal weight; MHAOW, metabolically healthy abdominally overweight; MUAOW, metabolically unhealthy abdominally overweight; MHAO, metabolically healthy abdominally obese; MUAO, metabolically unhealthy abdominally obese.

Weighted kappa (95%CI), measuring agreement between two classifications, was 0.667 (0.660- 0.674)

Figure S1. Schematic representation of the EPIC-CVD case-cohort design and sample included in the complete-case analysis

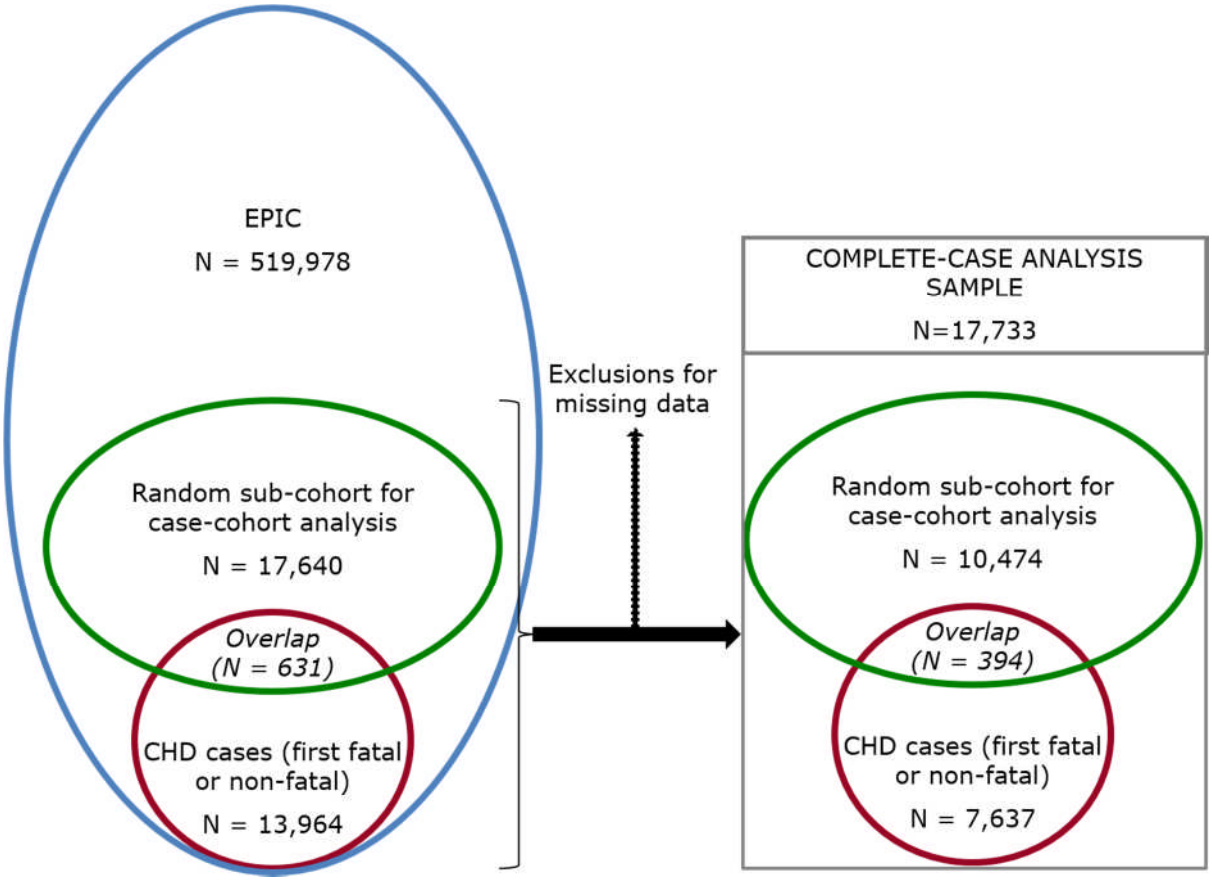


Figure S2. Schematic representation of the analysis strategy

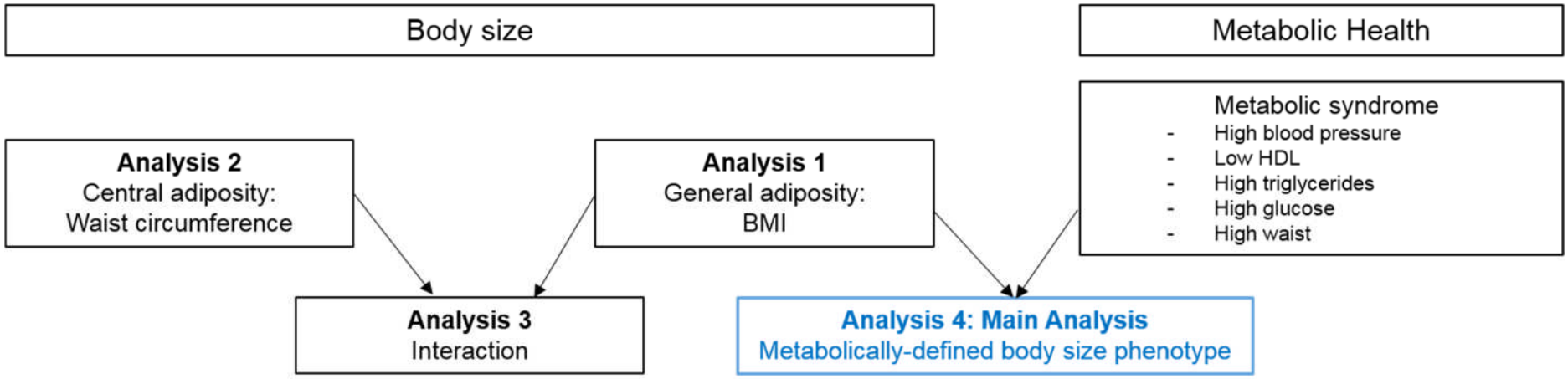
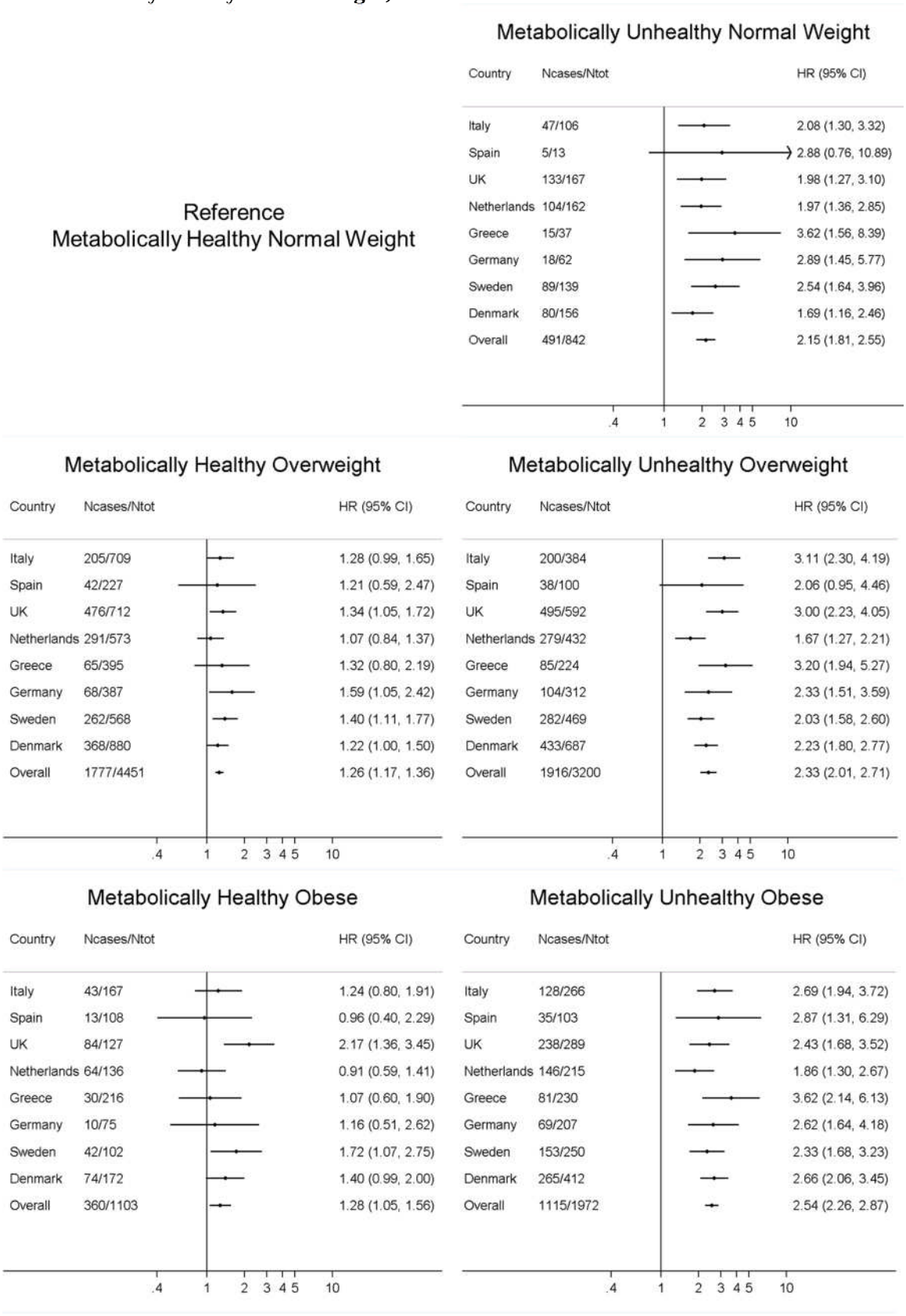
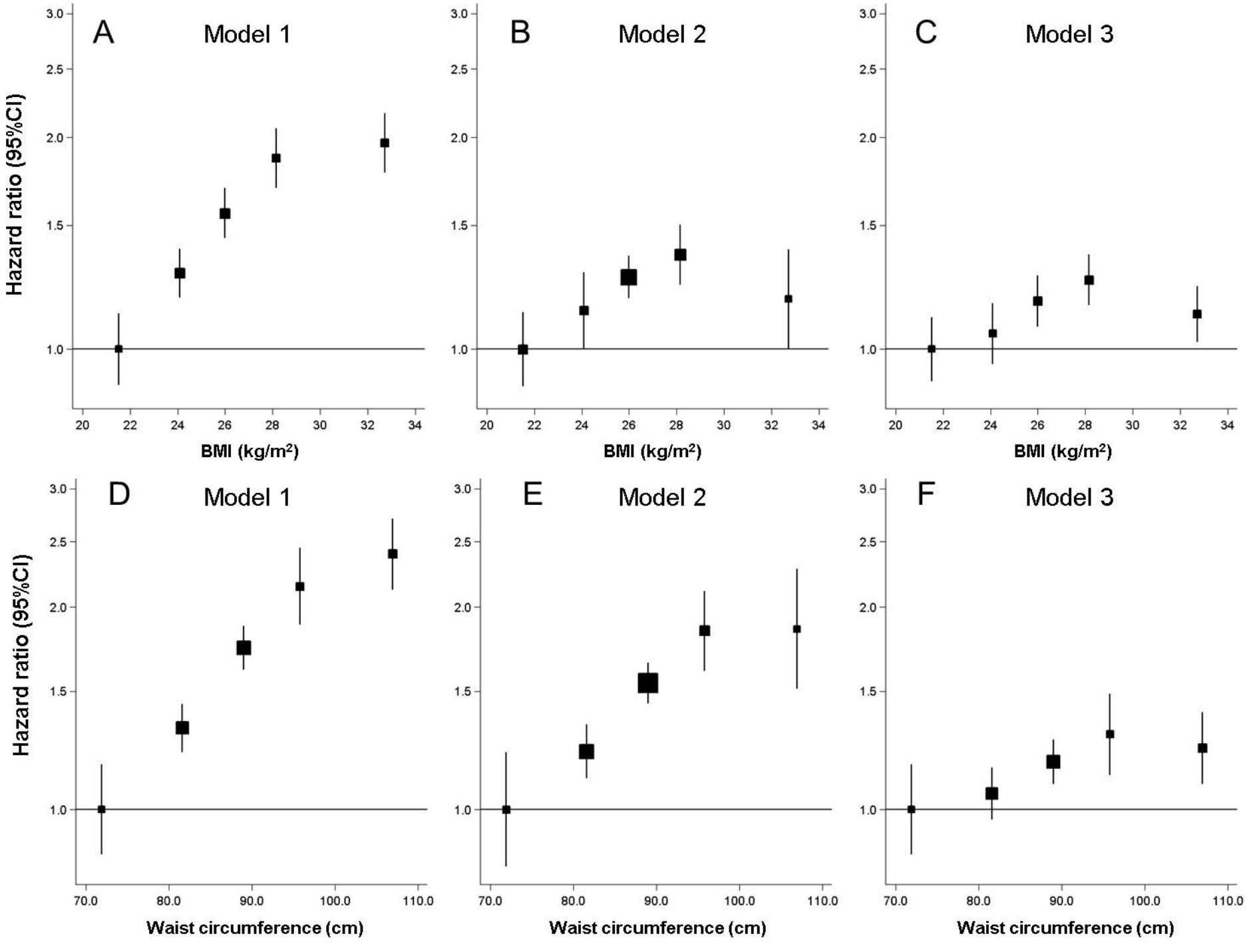
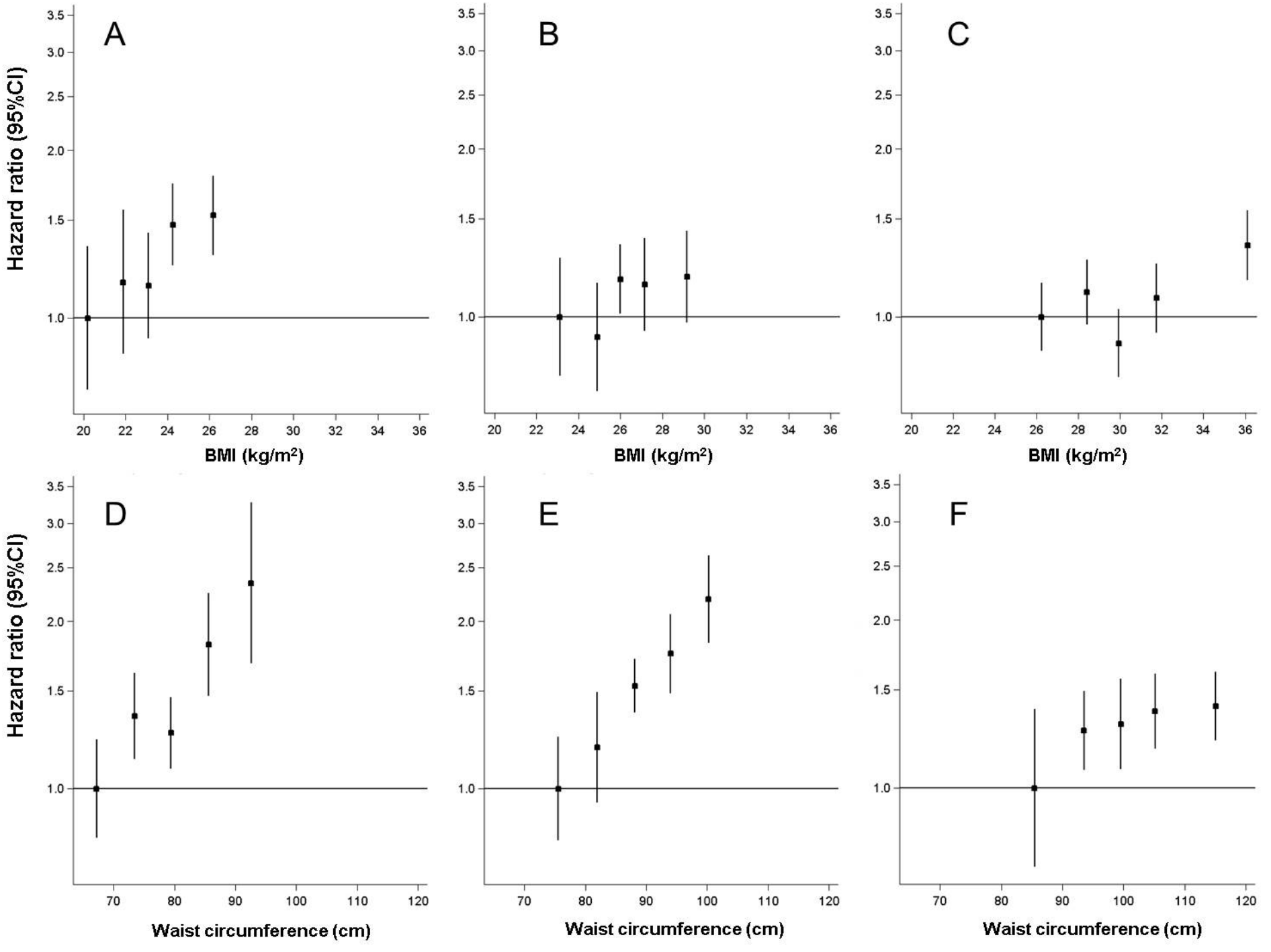


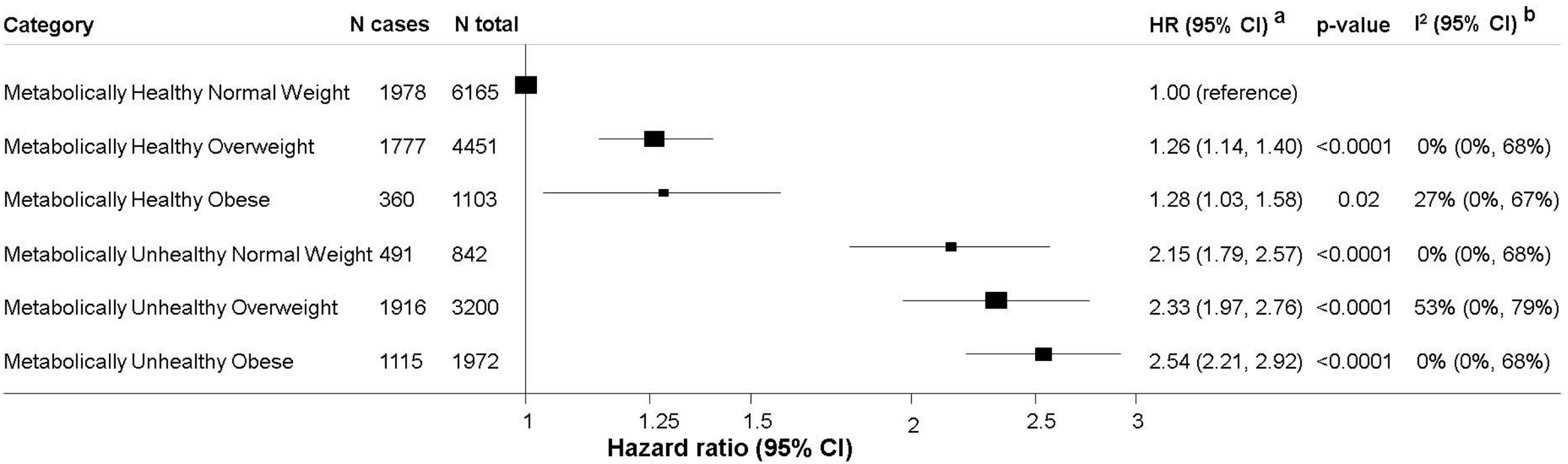
Figure S3. Country-specific HRs across metabolically-defined body size phenotypes compared to metabolically healthy normal weight, Model B [a]



[a] Model B was adjusted for age, smoking, educational level, physical activity, Mediterranean diet score, energy and alcohol intake


A
Model 1
B
Model 2
C
Model 3
D
Model 1
E
Model 2
F
Model 3
Hazard ratio (95%CI)
Hazard ratio (95%CI)
3.0
2.5
2.0
1.5
1.0
20
22
24
26
28
30
32
34
BMI (kg/m²)
BMI (kg/m²)
BMI (kg/m²)
70.0
80.0
90.0
100.0
110.0
Waist circumference (cm)
Waist circumference (cm)
Waist circumference (cm)


A
B
C
D
E
F
Hazard ratio (95%CI)
Hazard ratio (95%CI)
3.5
3.0
2.5
2.0
1.5
1.0
20 22 24 26 28 30 32 34 36
BMI (kg/m²)
70 80 90 100 110 120
Waist circumference (cm)


Category
N cases
N total
HR (95% CI) a
p-value
I² (95% CI) b
Metabolically Healthy Normal Weight 1978 6165 1.00 (reference)
Metabolically Healthy Overweight 1777 4451 1.26 (1.14, 1.40) <0.0001 0% (0%, 68%)
Metabolically Healthy Obese 360 1103 1.28 (1.03, 1.58) 0.02 27% (0%, 67%)
Metabolically Unhealthy Normal Weight 491 842 2.15 (1.79, 2.57) <0.0001 0% (0%, 68%)
Metabolically Unhealthy Overweight 1916 3200 2.33 (1.97, 2.76) <0.0001 53% (0%, 79%)
Metabolically Unhealthy Obese 1115 1972 2.54 (2.21, 2.92) <0.0001 0% (0%, 68%)
1
1.25
1.5
2
2.5
3
Hazard ratio (95% CI)